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Symposium on disorders in growth arising from renal tubular dysfunctions; introduction and commentary on renal rickets

Wallace W. McCrory, M.D.*

IOWA CITY, IOWA

DURING the last two decades considerable new and precise information has become available in the field of renal physiology. With these advances in our basic knowledge, it has become practicable to assess individually the integrity of many specific tubular functions. The recognition of discrete clinical disorders that are attributable to a deficiency or absence of one or more specific tubular functions has proved to be a most rewarding area for clinical investigation. We have, however, witnessed as a result of such efforts the accumulation of a bewildering number of so-called tubular syndromes. The descriptions of clinical syndromes attributable to tubular dysfunctions include considerable overlapping in respect to their diagnostic, clinical, and laboratory features. For example, one type of tubular dysfunction, renal acidosis, may be described as an eponymic syndrome (Butler-Albright syndrome or Lightwood syndrome), as a pathologic entity (hypophosphatemic rickets with nephrocalcinosis and lithiasis), as a functional syndrome (hyperchloremic, hypophosphatemic rickets), or as a renal tubular syndrome (chronic renal tubular acidosis).

The distinguishing clinical features arising from biochemical disorders initiated by many types of renal diseases are an expression of, and will depend on, the severity and number of alterations produced in the specific parameters of renal function. Functional depression of a particular transport process of renal function, such as tubular phosphate reabsorption or base conservation, will produce a similar characteristic pattern of metabolic alteration even though a number of different etiologic agents may be implicated in the pathogenesis of the dysfunction. While

**Address, Department of Pediatrics, State University of Iowa, University Hospitals, Iowa City, Iowa.*

it is true that some of the tubular syndromes are characterized by pathologic involvement of only one locus in the nephron, this is by no means the case in all of the tubular syndromes. In order that some of the common features of these disorders be appreciated whether the syndrome is present as an isolated defect or as an assortment of tubular dysfunctions, it would seem worth while to approach this subject matter from some generally applicable morphophysiologic basis. We will attempt this worthy endeavor and consider disorders of growth of renal origin from three vantage points: (1) those associated with inadequacy of renal mechanisms for base conservation, (2) those associated with alterations in one or more proximal tubular functions, and (3) those associated with alterations in distal tubular functions.

It is now generally recognized that disorders of growth due to renal disease may result either from inadequate renal excretory function *(renal retention)* or abnormal excretion of metabolites by the nephron *(renal wasting)* without associated significant reduction in the glomerular filtration rate. The term "glomerular insufficiency" has been suggested as applicable to the former and "tubular insufficiency" to the latter. This gross differentiation, while figuratively appealing, has many inadequacies. Glomerular insufficiency is a relative, not absolute, physiologic state, and it is most often accompanied in the presence of disease by variable degrees of tubular malfunction. Tubular function is normally closely integrated with and dependent on the process of normal glomerular filtration. Thus, such a distinction separating glomerular from tubular function is physiologically and pathologically awkward and artificial. The kidney of man is dependent for its normal function on the separation by filtration of a large volume of normal extracellular fluid. This ultrafiltrate of plasma then is available for alteration by tubular reabsorption, ion exchange, and excretion. If there are significant alterations in the composition, volume, or flow of glomerular filtrate this will invariably alter conditions for subsequent tubular perfusion, and complex changes occur as a result in renal excretory functions. Thus, glomerular-tubular imbalance is itself one cause of tubular dysfunction. The large filtered load provided in the normal kidney to the nephron population poses a unique physiologic opportunity for the unlimited and unnatural loss from body fluids of many minerals and metabolites if normal tubular transport mechanisms required for their recapture are inefficient or impaired.

The clinician must distinguish whether disorders are due to renal retention or renal wastage. The therapy of disturbances resulting from renal retention will require that therapeutic measures be aimed at the reduction or decrease of daily intake of specific metabolites or electrolytes until the excretory capacity of the kidney for this substance can be improved. Metabolic disorders due to renal wasting, on the other hand, require supplementation or increase of intake of the involved metabolite for correction. Both types of disturbances may and do coexist, such as salt-losing nephritis in preuremic patients. It is important to realize that these two conditions should not be considered as mutually exclusive.

GENERAL COMMENTARY ON RENAL RICKETS

With the advances made in the knowledge and practice of infant nutrition, we have witnessed the virtual disappearance of classical rickets due to dietary mineral and vitamin D deficiency. Endogenous metabolic disturbances are now the commonest cause of rickets, particularly as seen in older children (so-called late rickets). Alterations in calcium and phosphorus homeostasis of renal origin are certainly one of the commonest causes for rickets encountered in clinical practice in the United States today. A type of rickets that is indistinguishable, radiographically and biochemically, from true rickets occurs in association with certain of the tubular dysfunctions (i.e., renal tubular acidosis, Fanconi's syndrome). Although this type of rickets may be resistant to correction with usual vitamin D therapy, it should be

distinguished from the much more common form of D-resistant rickets with a familial history that occurs without any other evidences of renal dysfunction.[1] It is not at all clear that this latter type of rickets should actually be classed as a primary renal tubular dysfunction on the basis of presently available evidence. Children with these forms of metabolic rickets, if unrecognized or untreated during the growing period, will develop variable degrees of stunting and at times marked skeletal deformity. The term "renal rickets" would appear to be most appropriate for this condition. This would be true except that historically the use of this term has not been restricted to those cases showing a truly rachitic type of renal osteodystrophy. This term has been applied to a less common but interesting group of children with diverse forms of chronic renal disease[2] associated with stunting and skeletal deformities and radiographic bone changes similar, but not identical, with those seen in rickets. Children with this latter type of renal insufficiency usually show bone changes similar to those found in patients with chronic hyperparathyroidism (osteitis fibrosa) as well as some findings typical of rickets. This osteodystrophy seems to be the combined result of demineralization due to parathyroid hyperfunction stimulated by retention of phosphorus, poor dietary calcium intake in these chronically ill patients, and increased fecal and urinary loss of calcium because of uremia and chronic acidosis. Albright[3] considered cases with this type of bone disease to be instances of osteitis fibrosa rather than rickets. Children with renal disease associated with sufficient depression of the glomerular filtration rate to result in persistent hyperphosphatemia will have pleomorphic bone disease that represents a combination of changes seen in osteoporosis, rickets, and osteitis fibrosa, with the latter usually predominating.[4] Since the therapy and prognosis in the individual case varies greatly depending on the nature of the underlying renal disease, an accurate diagnosis of the type of osteodystrophy is imperative. The differential diagnosis of the bone changes of rickets, osteoporosis, and osteitis fibrosa can be aided greatly if the physician recalls that the health of the bone structure in any particular patient at a given time is the net resultant of the interplay of three distinct metabolic processes, deposition of bone matrix, subsequent calcification and conversion into normal bone, and resorption of bone.

Osteoporosis occurs as a result of a failure of production and deposition of adequate protein bone matrix. This is not a disturbance in calcium and phosphorus metabolism. The matrix that is deposited is normally calcified. The serum levels of calcium, phosphorus, and alkaline phosphatase are normal. The condition occurs as a result of growth failure whether due to malnutrition (inadequate protein intake) or uremia. It can also be seen with hyperadrenocorticism and with atrophy of immobilization or disuse. Patients with chronic renal disease consequently have many opportunities to develop osteoporosis.

Rickets develop whenever bone growth occurs without the presence of adequate amounts of calcium and phosphorus for the normal calcification of osteoid. The bone changes vary from those of demineralization to those of marked rickets. The serum phosphorus level is subnormal, the serum calcium may be normal or low, and the alkaline phosphatase value is elevated. The signs of rickets will be most pronounced in those children with the most active rate of growth, since rickets does not develop when growth is arrested.

Osteitis fibrosa is characterized by a generalized demineralization of bone with a decrease in bone tissue due to excessive resorption of bone stimulated by increased secretion of parathyroid hormone. The resorbed bone is replaced by noncalcified fibrous tissue. This process contributes to the occurrence of the typical epiphysial lesions and the woolly, moth-eaten appearance of the bones that is seen in children with renal osteodystrophy.[4] When hyperparathyroidism is secondary to renal failure, the serum phosphorus level is elevated, the serum calcium is low or normal, and the alkaline phosphatase level usually is increased.

The treatment of the bone disease is secondary to the treatment of the underlying renal disease. An accurate diagnosis of the type of renal dysfunction is essential if therapy is to be of any lasting benefit. The principles of such therapy have been reviewed recently[5] and are discussed more fully in subsequent sections of this review.

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I. Growth disorders associated with renal acidosis

Wallace W. McCrory, M.D.*

IOWA CITY, IOWA

PERSISTENT metabolic acidosis has long been recognized as one of the common manifestations of renal insufficiency. Considerable clinical interest has been generated by reports appearing in the past few decades describing acidosis of renal origin occurring without significant azotemia or other signs of impairment of glomerular filtration. This isolated disturbance has been called "renal tubular acidosis" to distinguish it from that seen with azotemia, so-called "uremic acidosis."

Butler, Wilson, and Farber, in 1936,[1] reported the occurrence of persistent unexplained acidosis with hyperchloremia in 4 infants who had no underlying renal disease or any history of significant abnormal losses from vomiting or diarrhea. All of the infants had a similar clinical history of failure to thrive, anorexia, and recurrent bouts of mild vomiting. All of them ultimately developed signs of marked dehydration and hyperpnea that led to clinical recognition of the disturbance. All of these infants died, and calcification of variable degrees was found in the renal medullary parenchyma at postmortem. These authors included in this report a description of a similar biochemical disturbance (hyperchloremic acidosis) observed in a 10-year-old boy who presented a different clinical course. The latter patient had a history of rickets which had developed at 1½ years of age, and he had subsequently failed to thrive or grow normally. The patient was dwarfed and had radiologic evidence of osteoporosis and rickets. There was diffuse nephrocalcinosis and lithiasis as well. No explanation of these findings was offered. At about the same time attention was called to the unusual finding of nephrocalcinosis in some infants at autopsy by Lightwood[2] in England. This report did not relate the nephrocalcinosis to any biochemical disturbance in infants. In 1939 Hartmann[3] called attention to the fact that renal acidosis could occur in the absence of other manifestations of renal disease. He described an infant whose clinical picture was similar to that described by Butler and colleagues. The only biochemical abnormality in this infant was persistent hyperchloremic acidosis. He considered the acidosis to be of renal origin and attributed it to defective tubular reabsorption of bicarbonate because the pH of urine (7.2 to 7.4) was similar to that of blood instead of being low as would be expected in the presence of marked acidosis. There was no association of rickets or calcinosis in this infant. Treatment of this infant with alkali resulted in prompt correction of the acidosis, but prolonged alkali therapy was required to prevent its recurrence. After a period of alkali therapy the infant apparently recov-

*Address, Department of Pediatrics, State University of Iowa, University Hospitals, Iowa City, Iowa.

ered completely. In 1940 Albright and coworkers[4] reported results of elaborate metabolic studies on an older child originally described by Butler, and on an additional case. These authors demonstrated that these patients showed little or no increase in titratable acid excretion or ammonia production when they were given anion loads as ammonium chloride. In accord with the then current concepts of the mechanisms of base conservation by the kidney, they postulated that this form of renal acidosis was due to defective capacity of the tubular mechanisms for excretion of acid urine and ammonium. Although their first cases had rickets, nephrocalcinosis, and nephrolithiasis, they observed similar cases subsequently in which renal acidosis occurred without the latter complications.[5] There is now general agreement that rickets and nephrocalcinosis represent complications of disturbed calcium homeostasis rather than primary defects in this disorder. Latner and Burnard[6] clearly demonstrated that infants with renal tubular acidosis had impaired bicarbonate reabsorption. They reported that the infusion of phosphate to infants with renal acidosis resulted in an augmentation in the rate of excretion of titratable acid and ammonium. Consequently, they ascribed the basic defect to faulty bicarbonate reabsorption rather than to defective acidification. They assumed that the defect involved the proximal tubule. Considerable controversy has occurred over the nature and location of the basic tubular dysfunction, i.e., whether due to faulty bicarbonate reabsorption or failure to excrete titratable acid or ammonium. In terms of present-day thinking, these views are no longer as mutually exclusive as was originally thought.

The clinical pattern observed in infants with this defect has been described in numerous reports.[6-10] The clinical course in infancy differs from that observed in older children and adults.[10-12] Reports of long-term follow-ups[7, 13] indicate that complete recovery can occur in the infantile type if diagnosis is prompt and proper treatment is instituted. Although attention has been called to the occurrence of this disturbance as a clinical entity due to a single tubular dysfunction, it can be observed in association with evidences of other renal dysfunction. Some impairment in urinary concentrating ability is very common, particularly in older subjects, and in cases with associated renal potassium wasting states. A similar disturbance frequently is associated with renal diseases associated with general aminoaciduria (Fanconi syndrome and cystinosis,[14-16] and Lowe's syndrome[17]). Renal acidosis has long been recognized as a common complication of chronic renal insufficiency arising from a number of causes: nephritis, obstructive uropathy, polycystic disease of the kidney, and hypoplasia. The requirements for diagnosis and therapy of acidosis of renal origin are similar whether this distortion is encountered as an isolated entity or as one of a number of disturbances in renal function.

PHYSIOLOGIC CONSIDERATIONS

The normal adult ingesting a normal diet has a daily catabolic load of anion of 40 to 80 mEq. If normal acid base balance is to be maintained, this excess anion load must be excreted as "free" anion without so-called "fixed base" (sodium, potassium, calcium, and magnesium) with which it is combined in body fluids and glomerular filtrate. The elimination of such anion normally is achieved by its excretion as titratable acid or as an ammonium salt. There has been considerable argument as to whether renal tubular acidosis is the result of faulty bicarbonate reabsorption by the tubule or impaired acidification and ammonia excretion. It was previously thought that bicarbonate reabsorption, urinary acidification, and ammonia excretion involved physiologically separate processes located in different parts of the nephron. Bicarbonate reabsorption was considered to occur primarily in the proximal tubule and acidification and ammonia secretion in the distal tubule. Current concepts hold that all bicarbonate reabsorption involves sodium-hydrogen exchange and is qualitatively similar through-

out the nephron.[18] The process of acidification can best be described in operational terms as the exchange of sodium ions in the tubular lumen for hydrogen ions in tubular cells.[19] The effect of this exchange on the ultimate pH of urine depends on the composition of tubular urine at the exchange sites. As long as bicarbonate is present in tubular fluid, this exchange ultimately results in the further reabsorption of bicarbonate. When bicarbonate has been absorbed largely from tubular urine, the exchange of hydrogen ion for sodium involves other buffer salts, predominantly phosphate. It is by this process that acidification of the urine is achieved. Ammonia synthesized by tubular cells diffuses freely into tubular fluid. It can combine with hydrogen ion and then exchange with or replace other cations (sodium, potassium) and thus allow excretion of anion as a neutral ammonium salt. The amount of cation exchanged (conserved) by these two processes can be quantitated by measurements of urinary titratable acidity* and urinary ammonium. In a patient with defective bicarbonate reabsorption and hydrogen ion secretion, the conservation of base accomplished by excretion of free anion would be impaired, and buffer base (sodium, potassium, calcium, and magnesium) would be lost with anion. The consequent wasting of bicarbonate and loss of cation will eventually lead to metabolic acidosis and to a decrease in plasma bicarbonate.

The defective excretion of ammonium in patients with renal acidosis could be due to either a primary failure in ammonia synthesis or a secondary result of decreased diffusion secondary to diminished acidification of the urine. Ammonia is thought to diffuse more freely into an acid urine. The reported increase in excretion of titratable acid and ammonia observed in patients with renal tubular acidosis following infusion of suitable phosphate preparations[6] would suggest that the second mechanism is operative in some of these patients. It is conceivable that defective ammonia secretion due to disorders in ammonia-forming enzyme systems causes this disturbance in some instances.

The amount of hydrogen ion added to urine leading to formation of titratable acid is dependent on the pK' of the buffer available within tubular urine.[20, 21] The gradient of hydrogen ion against which this secretion occurs has physiologic limits. Normally the minimal pH of urine is approximately 4.5. Tubular secretion of hydrogen ion ceases normally when a gradient of this magnitude has been achieved. If the only buffers present in tubular urine have a low pK', the secretion of hydrogen ion would rapidly lower the pH of urine, and the total amount of hydrogen ion that could be excreted as titratable acid under these circumstances would be relatively small. In the case of phosphate (pK' 6.7), however, secretion of hydrogen ion has a relatively small effect on urine pH, and the total hydrogen ion excreted as titratable acid when phosphate is available can be large. In renal tubular acidosis the limiting hydrogen ion gradient can be considered to occur at a much higher pH than is true in the normal. Voided urines usually contain little titratable acid. Urine of a pH of 6.5 or higher will contain significant concentrations of bicarbonate. When one considers the process of acidification in these terms, it is understandable that the infusion of phosphate to patients with renal tubular acidosis could, by increasing the available phosphate buffer, result in the increase (quantitative) of titratable acid and ammonium excretion even in the presence of some impairment of the mechanisms of sodium-hydrogen ion exchange.

One aspect of the abnormalities found in tubular functions as a result of potassium depletion deserves mention here (see also Section III on Disorders of the Distal Nephron). The ability of the patient depleted of potassium to increase urinary titratable acidity after ingestion of anion

*Titratable acidity of urine actually represents the amount of base (equivalent to sodium, potassium, calcium, and magnesium) required to "titrate" acid urine back to the pH of glomerular filtrate, i.e., pH 7.4.

loads (ammonium chloride) is less than that of normal subjects. The kidney of the patient with potassium depletion is unable to produce a highly acid urine.[22] This defect results from the inability of the tubule to achieve the normal maximal concentration gradient of hydrogen ion between urine and plasma. This defect is not due to a limitation in sodium-hydrogen ion secretion. The amount of sodium and bicarbonate resorbed and hydrogen ion secreted by the renal tubule in the presence of potassium depletion actually is increased.[23] As a consequence, in the presence of potassium deficiency a greater proportion of hydrogen ion is excreted as ammonia and less as titratable acid. Ammonia excretion is unimpaired in these patients, and it increases normally in response to acid loads. This alteration in tubular function maintains the extracellular alkalosis with the increase in plasma bicarbonate concentration. The urine passed is usually acid in reaction despite the presence of alkalosis, a phenomenon that has been termed the "paradoxical aciduria" of potassium depletion. Since acid metabolites must be excreted in those with potassium deficiency just as in the normal subject, this finding is actually neither paradoxical nor inappropriate. These alterations in renal function are corrected by potassium replacement therapy adequate to restore potassium balance to normal.[24] This renal functional defect can coexist with renal acidosis, and it should be kept in mind when tests are made of the acidification capacity of the kidney.

The administration of carbonic anhydrase inhibitors to human beings results in the development of hyperchloremic acidosis and the passage of alkaline or weakly acid urine. The similarity of the disturbance produced to that seen in tubular acidosis led to the postulation that the basic defect in tubular acidosis was a deficiency of this enzyme. The administration of carbonic anhydrase inhibitors to patients with renal acidosis[25, 26, 27] has, however, shown that they respond with a further increase in bicarbonate excretion typical of some degree of carbonic anhydrase inhibition. This evidence strongly suggests that in this disease a defect in the availability of carbonic anhydrase cannot be implicated as the sole factor limiting the acidification mechanism. One patient with renal acidosis has been reported to have normal carbonic anhydrase activity of tubular tissue removed by renal biopsy.[28]

Patients with renal acidosis in association with the aminoacidurias (Fanconi syndrome, cystinosis[14, 15]) and Lowe's syndrome[17] have qualitatively similar but less severe defects in tubular mechanisms for base conservation. The mechanism of acidosis in these disturbances is still somewhat obscure, however, and it does not appear that it can be attributed solely to tubular dysfunction involving the sodium-hydrogen ion exchange mechanism.

Considerable confusion exists in regard to the mechanism of renal acidosis in uremia. Distinctions have been made between renal tubular acidosis and uremic acidosis on the basis of differences in the composition of plasma. These differences have been further emphasized by attempts to divide them mechanistically into two types, one glomerular and the other tubular. The acidosis observed in renal tubular acidosis is usually characterized by an associated hyperchloremia with little or no elevation of blood urea nitrogen or nonprotein nitrogen. The acidosis seen in association with azotemia is characterized by an increase in plasma concentrations of inorganic phosphate, sulfate, and other organic acids and a normal or low concentration of chloride.

In the presence of marked reduction of the glomerular filtration rate and continued normal protein intake, the plasma concentration of these ions must rise because of endogenous catabolism in a manner similar to that of urea until the plasma level is sufficiently high to facilitate urinary excretion to keep up with the rate of accumulation. The concentration of cation in plasma (mainly sodium) is normally independent of pH and is maintained within a fixed range by complex mechanisms acting

to maintain and preserve osmolarity of body fluids within fixed limits. Concentration of serum sodium consequently does not rise in acidosis unless dehydration is present or develops. Increases in the concentration of phosphate, sulfate, and other anions must consequently be offset by a depression of remaining anion, mainly chloride. These differences in the composition of plasma anion in acidosis found with renal disease thus depend largely on the presence or absence of an associated decrease in the glomerular filtration rate.

It has long been recognized that the basal excretion of ammonium may be reduced greatly in patients with chronic renal insufficiency of any cause. These patients fail to show increased ammonia excretion that is normally seen in response to exogenous or endogenous acidosis. Recent studies of tubular function in patients with chronic renal disease[27, 29] indicate that there is defective reabsorption of bicarbonate and deficient excretion of titratable acid as well in many of these patients. As has been pointed out by Schwartz,[29] we should regard all instances of acidosis due to renal disease as manifestations of common defects in certain tubular functions. Acidosis due to renal disease can only result from (1) loss of excessive base as bicarbonate in the urine due to failure of normal renal tubular bicarbonate conservation, (2) impaired renal tubular excretion of hydrogen ion (acid) either as ammonium salts or titratable acid, or (3) a combination of both defects. The relative functional importance of defects in bicarbonate reabsorption or ammonia formation may vary in each type of renal disorder.

ETIOLOGY

The cause of renal acidosis in those instances where there is no other underlying renal disease (i.e., idiopathic or primary renal tubular acidosis) is unknown. The hypothesis that mild urinary tract infection in infants could be a cause is most appealing. Such an acquired lesion theoretically could be reversible with effective treatment. The preponderant number of infants with this defect have not, however, been found to have convincing evidence of associated urinary tract infection.[7-10] The chronicity and lack of reversibility of the disease as seen in older children and adults suggest that in some instances congenital enzymatic tubular defects could be responsible. Descriptions of multiple cases in families[12, 30-32] lend further support to this hypothesis. It is conceivable that the medullary area of the kidney of the infant is peculiarly susceptible to hypoxic or toxic damage in the presence of severe circulatory and electrolyte imbalance. I have observed an instance of temporary renal acidosis occurring in an infant following an episode of profound shock, dehydration, and electrolyte imbalance due to gastroenteritis. Impairment of acidification mechanisms and concentrating ability was demonstrable after recovery but subsequently disappeared within a few weeks of the acute episode. In most reported cases, however, there is no history of such episodes prior to the clinical recognition of the disease.

The cause of the disturbances in calcium metabolism has not been defined clearly, but acidosis is considered to be the primary event. Mobilization of body stores of calcium occurs in response to acidosis. Hypercalciuria is considered a reflection of this affect.[5] It is quite likely that there is some degree of secondary hyperparathyroidism in cases showing more advanced calcium depletion. Hypercalciuria would facilitate the deposition of calcium salts in damaged nephrons in the kidney. The reason for the localization in the distal portions of the nephron, the collecting ducts, and the medullary area is not known. This localization is referred to as nephrocalcinosis to distinguish it from intrapelvic stone formation or lithiasis. Nephrocalcinosis can be observed in a variety of conditions of varied etiology and is not in itself pathognomonic of renal acidosis.[33] Although calcium deposition may occur in areas of tissue damage, it would in itself contribute to further extension of tubular dysfunction and may lead to complete renal insufficiency. Nephro-

calcinosis and lithiasis are rarely found in cases with primary generalized amino aciduria (Fanconi type, cystinosis). Precipitation of calcium salts is thought to be favored by an alkaline urine. The dietary intake of calcium and phosphorus and the concentration of certain solublizing anions (phosphate and citrate) in tubular urine, may also be important factors.[34]

Chronic potassium depletion may contribute to tubular dysfunctions in urinary concentrating capacity and in acidification. It can also result in morphologic and functional damage in the nephron (Section III).

CLINICAL CONSIDERATIONS

The clinical manifestations of chronic acidosis of renal origin are predominantly those of growth failure. Although cases occurring in the first few months of life have been described, the disease more commonly becomes symptomatic after a few months of apparently normal growth. Symptoms may often appear after the weaning period. The afflicted infant develops progressive anorexia, especially for solid foods and for formula. Thirst, as evidenced by willingness to drink low solute liquids (water, juices, etc.), is, however, often maintained. Recurrent episodes of vomiting occur and the infant fails to show progressive gains in weight. Constipation may be noted. The infant may continue to void freely. Medical help may be sought because of failure to thrive. Alternatively, medical help is sought when the patient develops marked dehydration with persistent vomiting for no apparent cause. The presence of metabolic acidosis can be detected by appropriate biochemical studies of the blood. Serum bicarbonate concentration will be decreased, as will pH, and serum chloride increased, while blood urea nitrogen or nonprotein nitrogen is usually within the normal range except during periods of serious dehydration when it may be elevated transitorily. The likelihood that the acidosis is of renal origin is great if the urine obtained simultaneously fails to show the low pH (less than 6.0) which is expected if renal function is adequate in the presence of metabolic acidosis from any cause. An additional suggestive finding would be the failure of urine specific gravity to be as high (greater than 1.018) as expected if renal concentrating ability were normal in the presence of dehydration. The urine usually contains small quantities of protein, and some increase in white blood cells may also be found. Urine cultures occasionally reveal the presence of significant pathogens.

The findings listed above are not in themselves diagnostic because they may occur in association with disturbances of renal function resulting from severe dehydration and acidosis from a variety of causes. The diagnosis of renal acidosis depends on the observation of the infant after proper treatment for the correction of acidosis and dehydration. If the infant again develops metabolic acidosis spontaneously after recovery and continues to pass urine that is alkaline or at most weakly acid, the diagnosis of renal acidosis is established. Suitable studies then should be carried out to determine whether this abnormality is the sole manifestation of renal malfunction.

In cases occurring beyond the age of infancy, the signs usually appear insidiously. The symptoms (anorexia, recurrent vomiting, dehydration, etc.), although less pronounced, are similar. Growth failure may be evident as dwarfism. Polyuria and polydipsia are quite characteristic in the older subjects. Chronic acidosis is associated with a drain of the body stores of calcium and potassium. Attacks of unexplained weakness may occur in patients who have an associated renal potassium losing state. Nephrolithiasis may be responsible for the presenting symptoms, but this rarely occurs in the first decade. Disturbances in bone growth are quite characteristic of this type of renal acidosis. "Late rickets" (onset after 1 year of age) is often seen and, if untreated, may progress to produce severe deformities (genu varum and valgum). These deformities may be the presenting complaint of the patient. The diagnosis of renal acidosis is established in the same

manner in these subjects as is the case in infants.

In patients with calcium depletion and rickets, hypophosphatemia is common as is elevation of activity of blood alkaline phosphatase. Serum calcium is normal. Radiologic signs of rickets or osteomalacia can be seen in such cases. Abdominal roentgenograms may show the presence of nephrocalcinosis. In patients with more advanced forms of the disease, quantitative assessment of renal acidification and base conservation mechanisms are not necessary. When the diagnosis is equivocal, however, the patient's capacity for urinary acidification and ammonium excretion can be tested. After collection of urine obtained under control conditions with the patient receiving a normal diet, ammonium chloride (75 mEq. per meter^2 surface area per day) can be administered orally. This anion load, if continued for 2 to 3 days, normally will induce a marked increase in titratable acid excretion and urinary ammonia excretion and cause only a slight lowering in plasma bicarbonate concentration. It should be remembered that this test procedure will cause exaggeration of any existing metabolic acidosis, and the patient's response to the test should be observed carefully. A single dose with a short period of observation may prove to be as useful.[13] The acute renal response to a single dose of acetazolamide has also been used and compared with that observed in normal controls.[27]

There are insufficient available data to allow one to generalize regarding the normal limits for daily outputs of titratable acid and ammonium in infants and children. The response of the patient can best be judged by comparison with that of a suitable normal control similarly observed.

It is not always necessary to define quantitatively the patients' renal capacity for acidification and ammonium excretion to establish the diagnosis. A patient showing persistent, unexplained metabolic acidosis with continued passage of alkaline or weakly acid urine, while ingesting a normal diet, can be considered to have renal acidosis.

The possibility that this disturbance represents only one of a number of tubular functional defects must be considered and investigated in all cases. Growth failure and renal acidosis may also be found in association with (1) Fanconi syndromes and cystinosis, (2) Lowe's syndrome, (3) obstructive uropathy, (4) hypoplasia of the kidney, (5) polycystic kidney disease, and (6) chronic nephritis and pyelonephritis.

TREATMENT

Treatment designed to correct the electrolyte disorder usually results in a remarkable disappearance of symptoms. Administration of alkali in doses adequate to correct the acidosis must be followed by maintenance therapy until there are clinical and biochemical evidences of recovery of defective renal function. Once the diagnosis has been established, initial therapy consists of providing alkali, either orally or parenterally, in amounts sufficient to elevate the serum bicarbonate concentration to levels between 20 to 25 mEq. per liter. Sodium citrate, lactate, and bicarbonate are all equally effective. The amount required for correction must be tailored to the needs of the individual case. Daily doses usually range from 30 mEq. of sodium per day for small infants to 180 mEq. of sodium per day for older children. Doses needed for maintenance are usually two-thirds to one-half of those needed for initial correction.

Dangers that may occur with corrective alkali therapy are of two kinds: (1) overdosage of alkali leading to alkalosis with the threat of alkalotic tetany and (2) failure to provide an adequate intake of solute-free water (other than milk or food) by administration of alkali in too concentrated a form. This leads to the development of hypertonic dehydration.

The frequency of the association of impaired urinary concentrating ability in renal acidosis has not been stressed adequately. The administration of the large doses of alkali needed for correction may actually overtax the patient's renal excretory ca-

pacity for solute. Albright's solution is 10 per cent sodium citrate. The kidney with defective concentrating ability requires an exogenous source of "free" water for the excretion of this solute load in dilute urine. Thus, even though the amount of alkali needed to correct the acidosis may be properly calculated, its administration without provision of adequate free water, for example, by adding 60 c.c. of Albright's solution to the infant's milk formula, may be associated with renal sodium retention and serious, or even fatal, hypertonic dehydration.[32] The serum sodium concentration should be observed serially and any elevations should be considered as an indication for either decreasing solute intake or increasing solute free water intake.

With the correction of the acidosis one observes a remarkable return of appetite, loss of listlessness, and return of progressive weight gain. The subjects must be followed at intervals with biochemical measurements to observe the status of blood electrolytes. When normal values for serum bicarbonate have been maintained for 1 to 2 months and all symptoms have been relieved, the maintenance dose of alkali can be reduced to see whether improvement in renal base conserving function has occurred. Infants may show complete recovery within 2 months or may require therapy for 2 years. Older subjects, with rare exceptions, require continuous maintenance therapy.

When rickets is also present, vitamin D and added calcium should be prescribed. The induction of healing of rickets is difficult unless the acidosis can be controlled. It would thus resemble vitamin D-resistant-rickets. Attempts at inducing healing by high dosage vitamin D and calcium therapy in patients with primary renal tubular acidosis may be dangerous until the acidosis has been controlled. Such therapy would increase the absorption of calcium and hypercalciuria and increase the likelihood of further deposition of calcium in the renal parenchyma. When the acidosis has been corrected, the rickets can be effectively treated. If one finds a rachitic state that appears to be resistant to vitamin D therapy after correction of the acidosis, he is probably dealing with renal acidosis associated with proximal tubular dysfunctions rather than primary renal acidosis.

PROGNOSIS

In the infantile forms without calcinosis or rickets, prognosis is excellent.[7-10, 13] In older children the outlook depends on the reversibility of renal damage at the time the patient is first seen. If calcinosis and lithiasis are extensive, little improvement can be expected. Further deterioration of renal function is inevitable, however, if acidosis is not controlled and hypercalciuria is maintained. Alkali treatment can improve greatly the clinical picture and arrest the progressive deterioration of renal function and should be tried vigorously. Prolonged alkali therapy does not appear to increase the danger of nephrocalcinosis or lithiasis. Dramatic clinical improvement may be observed in many of these subjects. The nephrocalcinosis is not usually improved, even with control of acidosis. In forms of renal acidosis associated with other renal tubular dysfunctions, in most instances the outcome will depend on the course of the associated disease.

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II. Growth failure due to diseases of the proximal tubule

Howard G. Worthen, M.D.*

MINNEAPOLIS, MINN.

DYSFUNCTION of the proximal tubules is being recognized with greater frequency as a cause of growth failure. A large number of syndromes have been described in which proximal tubular function is deficient, although not all of them produce growth failure. Dwarfism is the most common sign of this type of renal disease. In some of the proximal tubular syndromes, dwarfism can be ascribed directly to the disturbance in renal function, and therapy directed to the renal defect may lead to improvement in the growth rate. In other syndromes, no evident connection can be found between the tubular defect and the growth failure, and the demonstration of renal abnormality is useful chiefly as an aid in diagnosing the underlying defect.

PHYSIOLOGIC CONSIDERATIONS

The proximal tubule is responsible for the active reabsorption of a large number of substances from the glomerular filtrate. Defective proximal tubular function can therefore lead to the excessive loss of one or more of these substances into the urine. The substances which have received the most attention are glucose, amino acids, phosphorus, potassium, bicarbonate, sodium, and chloride.[1, 2]

Little is known of the chemical and physical mechanisms responsible for active tubular reabsorption or secretion. Although it appears probable that separate tubular transport systems exist for most substances, studies of competitive reabsorption[3] suggest that more than one substance may be transported by some reabsorptive systems. Reabsorption is presumed to be a multi-stage process and to be under enzymatic control.[4] The reabsorption of glucose, amino acids, and phosphate appears to occur predominantly in the first half of the proximal tubule. Lesions of the first portion of the proximal convolution may cause abnormal excretion of all of these substances. Since the locus for maximal reabsorption of glucose, phosphate, and amino acids is probably not identical, different inhibitory effects may be produced by lesions occurring at different anatomic levels. The reabsorption of sodium, chloride, bicarbonate, and potassium is thought to occur uniformly through-

From the Pediatric Research Laboratories of the Variety Club Heart Hospital, University of Minnesota.

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**Address, Pediatric Research Laboratories of the Variety Club Heart Hospital, University of Minnesota School of Medicine, Minneapolis 14, Minn.*

out the proximal tubules, and lesions in the proximal tubule also may adversely affect electrolyte excretion. Attempts at localization of defects of electrolyte excretion are complicated by the activity of the distal tubule which also resorbs sodium, chloride, and bicarbonate and secretes potassium.[5] The specificity of an enzymatic defect may vary. Alteration in an energy-yielding enzyme system might reduce reabsorption of many substances or affect only a single substance. Even when a single transport system is affected, variations in the severity of the defect are possible. Decreased reabsorption is not necessarily indicative of severe impairment of transport mechanisms. A reduction in threshold for excretion may be present without a concomitant reduction in maximal resorptive capacity (Tm). Studies have been reported in patients in whom reabsorption of glucose[6] or bicarbonate[7] was incomplete at low plasma levels but in whom the Tm was normal. Such discrepancies might be due to a few abnormal tubules scattered among the normal ones (heterogeneity of the nephrons) or to a change in the rate of transfer involving all nephrons.[6] The stepwise nature of tubular transport suggests that reabsorption can be depressed at more than one step. Secretion of PAH can be inhibited at two different steps.[8]

The interpretation of the mechanism responsible for defective tubular transport is further complicated by the fact that extrarenal factors modify tubular activity. As an example of the difficulties encountered in trying to separate renal from extrarenal factors, one need only attempt an interpretation of the mechanism of phosphaturia. The long-standing dispute regarding the mechanism of action of parathyroid hormone apparently has been settled by the conclusive demonstrations that parathyroid hormone does depress phosphate tubular reabsorption and Tm,[9, 10] so that fluctuations in parathyroid activity will induce alterations in phosphate clearance and Tm. In addition, the phosphorus intake influences the phosphate Tm, an effect which is at least partially independent of the parathyroid glands.[11] Acidosis lowers the threshold for phosphorus excretion without depressing the Tm[12]. The interplay of these effects in combination with inhibition of phosphate reabsorption by glucose, amino acids, hypokalemia, and cortisone[13] makes the assessment of phosphaturia difficult. Because of the large number of factors that are capable of inducing alterations in tubular transport, it is often impossible to be certain of the nature of tubular defects in some of these syndromes. Fortunately, however, the requirements for clinical diagnosis are not as difficult as they might appear. The renal tubular defects present in the "proximal tubular" syndromes are sufficiently consistent so that their presence can be predicted fairly accurately on the basis of certain typical clinical and laboratory findings.

LABORATORY AIDS TO DIAGNOSIS

The laboratory studies needed for the diagnosis of proximal tubular dysfunctions can be performed by most routine biochemical laboratories. The presence of glycosuria without hyperglycemia, systemic acidosis with a neutral or alkaline urine, hypophosphatemic rickets refractory to correction with normal doses of vitamin D, or idiopathic hypokalemia indicates the need to consider the existence of a proximal renal tubular dysfunction. One of the principal obstacles in the routine diagnosis of these syndromes has been the difficulty of demonstrating the presence of aminoaciduria. This is one of the most sensitive indicators of proximal tubular disease. A simplified chromatographic method for the qualitative detection of significant aminoaciduria without complicated special equipment has been described recently.[14]

The exact definition of the type and severity of proximal tubular transport dysfunction requires quantitative measurements of excretion rates for the assessment of renal function. Active reabsorption or secretion requires the expenditure of energy to trans-

port the substance against a concentration gradient. The rate at which such transport occurs is limited. The maximal or limiting rate is defined as the Tm for the particular substance. The determination of the Tm for a substance is the most specific and reproducible means of quantitating a particular tubular transport capacity. The rate of tubular resorption of glucose, phosphate, and amino acids found in the presence of normal or low plasma levels often differs from that found when the Tm for the same substance is determined. The determination of Tm for a particular substance requires that its rate of reabsorption be measured when the filtrate load has been increased by elevation of the plasma level so that the capacity of the tubular transport mechanism is exceeded. The determination of the secretory capacity can be used as another index of the integrity of proximal tubular function. Para-aminohippurate Tm (Tm_{PAH}) is the most satisfactory measure of proximal tubular secretory capacity. In such studies a simultaneous measurement of glomerular filtration rate is necessary for the calculation of the Tm of a substance. The clearance of inulin is generally accepted as a measure of the glomerular filtration rate. Studies on renal function of this type are so technically arduous that they are used mainly as research techniques. Modified clearance tests can be performed, however, that will provide the clinician with accurate information concerning specific aspects of tubular function. Such information is valuable for accurate diagnosis, as a base line for evaluation of therapy and for considerations of prognosis. The measurement of the endogenous creatinine clearance is a sufficiently accurate measure of the glomerular filtration rate so that it may serve as a substitute for the more accurate and involved procedure of measuring the inulin clearance. It is important that the methods used to determine plasma and urine creatinine be specific.[15, 16, 17] Most routine methods measure chromogens other than creatinine and these may give artificially high values, particularly for blood levels in young subjects.[15] The demonstration of excessive rates of renal excretion of glucose, amino acids, phosphate, or other metabolites can be obtained by estimating their clearance simultaneously with the measurement of the endogenous creatinine clearance. This study can be performed without elaborate equipment. One must collect an accurately timed urine specimen, usually by catheterization, unless the patient is very cooperative. The exact duration of the collection period and volume of the urine specimen must be known in order that the rate of urine flow may be calculated. Blood samples are drawn at the start and finish of the urine collection period. The clearance for the particular substance in cubic centimeters per minute is then calculated by dividing the excretion rate in milligrams per minute by the average plasma level in milligrams per cubic centimeter. The clearance rate can then be expressed as the percentage of the creatinine clearance. The higher the value of the ratio obtained the greater is the inhibition of the rate of tubular reabsorption of the substance.

The same urine specimen can be used for measurements of pH, titratable acidity and ammonia excretion in order to evaluate acid-base regulating mechanisms. The bicarbonate and pH should only be measured in urine that has not been exposed to air. This can be accomplished most easily by having the urine collected under mineral oil. Another procedure not commonly performed in routine laboratories is the determination of amino acid concentration. The amino acid level can be measured with reasonable accuracy by several chemical methods[18] or by paper chromatography.[19]

ETIOLOGIC CONSIDERATIONS

Four principal mechanisms have been proposed to explain the various proximal tubular disorders.

Many of the syndromes appear to be the result of hereditary defects in a transport system of the proximal tubule. The limita-

tion of the transport defect to a single substance or a few chemically related substances, the absence of other abnormalities which might damage the tubule, and the stability of the defect all favor the possibility that an intrinsic abnormality of the tubule is responsible for the functional disturbance. Examples of this type of disorder are hereditary renal glycosuria,[2, 6] cystinuria,[20] glycinuria,[21] and xanthinuria.[22]

Another mechanism which has been suggested as a cause for tubular dysfunction is a structural abnormality of the proximal tubule. The defect might be a congenital failure of the tubule to develop sufficiently in length or complexity, or it might be the result of an acquired disease which specifically injured the proximal tubule.

Clay and others[23] found evidence of an anatomic defect of the proximal tubule in two patients with generalized proximal tubular incompetence (the Fanconi syndrome), and, although their finding has not yet been confirmed, this is the nonspecific type of segmental defect that one would expect to produce generalized dysfunction.

The third cause for tubular dysfunction is damage or inhibition by an external toxin. Poisoning with lead, mercury, phenol, and uranium salts[24, 25] has been shown to produce more or less generalized proximal tubular dysfunction, and experimental inhibitors have been used which cause either generalized dysfunction[26] or decreased reabsorption of a single substance.[3]

The fourth possibility is tubular inhibition by a toxin or inhibitor arising endogenously from a metabolic abnormality. The tubular lesion of galactosemia is an example of an abnormality produced by an endogenous toxin. The toxic basis of the tubular dysfunction is indicated by the reversibility of the dysfunction when the inhibitor, presumably galactose-1-phosphate, is removed.[27] Other diseases which may be in this category are cystinosis,[19, 28] Wilson's disease,[29, 30] nephrosis,[31, 32] and multiple myeloma.[33] Two other diseases, in which no potential toxin has been found but in which the presence of an inhibitor is suspected, are the syndrome of infantile cirrhosis with proximal tubular insufficiency[6, 34] and Lowe's syndrome, in which the tubular disorder is accompanied by glaucoma and mental retardation.[35, 36, 37]

None of the isolated hereditary proximal tubular defects mentioned above is known to cause deficient growth, but two other syndromes, considered by some authors to result from isolated hereditary proximal tubular defects, do cause growth failure: vitamin D-refractory rickets and renal tubular acidosis.

Vitamin D-refractory rickets (phosphate diabetes,[1] renal hypophosphatemia[2]), is considered by many authors to represent a congenital inability of the tubules to reabsorb phosphate.[1, 38, 39] Patients with resistant rickets have a lower incidence of hypocalcuria, higher incidence of associated anomalies, and a narrower zone between the therapeutic and toxic doses of vitamin D than do patients with vitamin D-deficiency rickets.[39] These differences form the basis for the theory that the phosphaturia and hypophosphatemia result from an intrinsic tubular lesion, in contrast to vitamin D-deficiency rickets, in which secondary hyperparathyroidism is assumed to produce the phosphaturia. However, a much more cogent argument is the fact that some patients with refractory rickets have continued phosphaturia and hypophosphatemia, even though hypercalcemia is produced by treatment with vitamin D,[40] whereas phosphaturia disappears rapidly after vitamin D therapy in deficiency rickets. Even this argument is insufficient to support this theory because vitamin D itself produces phosphaturia in large doses,[41] and the persistent phosphaturia may be due to the massive amount of vitamin D necessary to promote calcium absorption in refractory rickets.

The most incisive studies on the pathogenesis of refractory rickets are those reported recently by Fraser and colleagues[42] and by Dodge and Daeschner,[43] using an infusion of calcium to avoid the complications inherent in the use of vitamin D. The administration of calcium intravenously

produced a striking decrease in phosphate excretion and an increase in serum phosphorus, without alteration of the glomerular filtration rate.

This response is the same as that seen in vitamin D-deficiency rickets and suggests that the pathogenesis of rickets and phosphaturia in both diseases is deficient intestinal absorption of calcium followed by secondary hyperparathyroidism.

More patients must be studied before this pathogenesis can be accepted for all cases, but present evidence must be considered to favor the interpretation that the hyperphosphaturia in vitamin D-refractory rickets is due not to an intrinsic tubular lesion but to a functional abnormality which occurs in response to deficient absorption of calcium. If this interpretation is shown to be correct, it might stimulate a renewed search for vitamin D analogues with greater dissociation of the calcium-absorbing and phosphorus-excreting effects.

The accepted treatment of refractory rickets without overt renal disease is still vitamin D, in a dose of 50,000 to 200,000 or more units daily, with careful supervision of the patient to prevent the occurrence of hypercalcemia. The provision of a high phosphate intake to replace that lost in urine shows some promise of improving the persistent hypophosphatemia.[44]

The cause of the phosphaturia occurring in patients with the Fanconi syndrome is even more controversial than in those with vitamin D–refractory rickets. The acidosis might be expected to cause reabsorption of bone and phosphaturia secondary to hyperparathyroidism, as has been suggested for renal tubular acidosis.[41] On the other hand, the presence of multiple reabsorptive abnormalities indicates that a severe proximal tubular defect is present, and phosphaturia might be expected from this alone. Our own studies[28] suggested that the lesion was intrinsic, because phosphate reabsorption did not improve when the serum calcium was raised with vitamin D. A large dose was used, and the phosphaturic effect of vitamin D might explain these results. However, the study of Fraser and associates,[42] using calcium infusion, demonstrated no improvement of the phosphaturia in one patient, indicating that overactivity of the parathyroid could not be implicated. Therefore it is assumed on the basis of present evidence that the phosphaturia is due to an intrinsic lesion, with the reservation that the number of studies is still too small to allow this theory to be accepted unequivocally.

CLINICAL PATTERNS OF PROXIMAL TUBULAR DYSFUNCTIONS

Growth failure caused by proximal tubular disorders may manifest itself either as acute cessation of growth in an infant in a manner similar to that which occurs in any acute, severe illness, or it may take the form of a chronic insidious stunting. The cause of the growth retardation is not known with certainty. The only documented cause is rickets, and the growth failure is most marked in the syndromes which produce rickets.

Fanconi syndrome with or without cystinosis. Some of the most striking examples of growth failure are seen in patients with the severe form of generalized proximal tubular incompetence (the Fanconi syndrome) which becomes manifest during infancy. This syndrome usually accompanies cystinosis,[19] but occasionally it may occur alone or with cirrhosis,[34] and 1 case has been described with glycogen storage disease of the liver and kidneys.[45]

During the first year of life, the symptoms generally consist of slow growth, irritability, anorexia, exaggerated reaction to infections, constipation, and motor retardation. Sometimes more specific symptoms are noted, such as polyuria, polydipsia, or an abnormal odor of the urine. The typical signs of rickets eventually develop, and the dwarfism is progressively apparent.

The laboratory findings are usually characteristic, so that the confirmation of the diagnosis is not difficult once the disease has been suspected. The presence of systemic acidosis with an alkaline urine,

glycosuria without hyperglycemia, aminoaciduria, hypokalemia, and hypophosphatemic rickets is diagnostic. Elevated rates for clearances of glucose, amino acids, uric acid, creatine, and phosphorus can be demonstrated.

When the renal disease is accompanied by cystinosis, the diagnosis is easier. Cystine crystals can be demonstrated in the cornea by means of the slit lamp and in the aspirate of bone marrow or excised lymph node by microscopic examination.[19]

The treatment of the Fanconi syndrome is still unsatisfactory. Intensive therapy with vitamin D to correct the rickets and sodium and potassium citrate to correct the acidosis and hypokalemia often produce marked symptomatic improvement, but the progression to renal insufficiency is probably not prevented. Bickel and associates[19] found that treatment of the rickets with large doses of vitamin D produced a decrease not only in the phosphaturia but also in the glycosuria and aminoaciduria. The effect of vitamin D therapy was confirmed by other workers[46] who suggested a beneficial effect of vitamin D on the tubular lesion. Others,[28] however, attributed this to the decreased glomerular filtration rate rather than to improved tubular function. The exact mechanism of action of vitamin D is unknown, and, although it exerts a salutary effect on the manifestations of the tubular disease, the long-term effect cannot be determined yet.

One fact which lends support to the thesis of Salassa and colleagues[46] that vitamin D might affect tubular functions other than phosphate reabsorption is that the aminoaciduria of vitamin D deficiency rickets is ameliorated by vitamin D therapy.[47]

Symptoms beginning early in life are the rule in two of the other diseases, galactosemia and Lowe's syndrome, which are accompanied by generalized proximal tubular dysfunction. In both of these disorders, however, the symptoms and the growth failure appear to be due largely to the extrarenal abnormalities.

Galactosemia. The patient with galactosemia usually becomes acutely ill shortly after the feeding of milk is begun. The usual symptoms are vomiting, marked lethargy, jaundice, and hepatomegaly. If the symptoms develop less acutely, growth failure, anorexia, and lethargy are generally found, accompanied by signs of hepatic dysfunction. Cataracts usually develop within 1 to 2 months. The diagnosis is usually made by demonstrating galactose in the urine.

Signs of tubular dysfunction are not usually manifest until the galactosemia has been present for at least a few days. The most common manifestations are proteinuria, aminoaciduria, hyperchloremic acidosis, and hypokalemia.

The acidosis and hypokalemia may contribute to the acute symptoms of the disease, but the presence of the proximal tubular defect otherwise has little effect on the outcome of galactosemia. The tubular dysfunction disappears when the galactosemia is controlled, so that no specific therapy is necessary.

Lowe's syndrome. Lowe's syndrome is generally evident at, or shortly after, birth. The appearance of the patient is typical; he is fat and flabby with hypermotility of the joints, enophthalmos, and congenital cataracts. Developmental retardation is present early and becomes progressively worse. The patient soon develops jerky, purposeless movements, a roving nystagmus, and a shrill cry.

The renal tubular dysfunction is manifest by the presence of albuminuria, aminoaciduria, organic aciduria, acidosis, and hypophosphatemic rickets. The effects of the tubular disease are relatively mild, and the rickets and acidosis can be controlled with small amounts of vitamin D and alkali.[35, 36, 37]

Syndromes with delayed onset of clinical manifestations. The generalized proximal tubular disorders which begin later in childhood usually produce less severe effects on growth. Five different etiologic types can be readily distinguished, although others undoubtedly exist. These five are the syn-

drome of idiopathic generalized proximal tubular insufficiency (the adult Fanconi syndrome occurring in both children and adults); Wilson's disease, heavy metal poisoning, particularly lead poisoning, the Fanconi syndrome in patients with malignancy, especially multiple myeloma, and nephrosis accompanied by the Fanconi syndrome.

The signs of the tubular disease are the same as in the types occurring earlier, including glycosuria, aminoaciduria, phosphaturia, hypophosphatemia, and acidosis without a strongly acid urine. The rickets of the infantile form is replaced by osteomalacia in the adult.[48]

The tubular lesion occurring in patients with Wilson's disease, multiple myeloma, and lead poisoning is of importance chiefly because it may aid in the diagnosis of the primary disease. The osteomalacia in Wilson's disease and multiple myeloma may be crippling, but it is usually reversible. Because of the severity of the liver and/or brain dysfunction in Wilson's disease and the malignant process in myeloma, the tubular dysfunction probably contributes little to the morbidity and mortality of these diseases.[33]

Acute lead poisoning in small children is such a severe disease that the renal lesion is usually disregarded, but the presence of glycosuria, acidosis, aminoaciduria, or hypophosphatemia may be helpful in suggesting the diagnosis of the lead poisoning in a patient with an atypical encephalopathy.

The Fanconi syndrome following nephrosis is of concern chiefly because the occurrence of the tubular dysfunction is evidence of severe prolonged proteinuria and, therefore, generally indicative of resistance to therapy. The generalized tubular dysfunction occurs late in the course of nephrosis, usually not until some degree of renal insufficiency is present, and is therefore associated with a poor prognosis.

In contrast to the preceding four disorders, the renal tubular lesion in patients with the idiopathic Fanconi syndrome is the primary concern.[45, 49, 50, 51] It is apparent that this diagnosis should be made only after excluding Wilson's disease, heavy metal poisoning, and malignancies, as well as cystinosis, since the tubular dysfunction might be the cardinal sign in any of these diseases.

The disease in older children is generally manifest by moderate to severe stunting, skeletal deformities, weakness, bone pain, and polyuria. The diagnosis is often suspected because of the discovery of pseudofractures, along with other changes of osteomalacia or rickets, and is confirmed by the typical laboratory findings and alterations in renal function. The results of replacement therapy may be quite dramatic, with complete disappearance of all symptoms, as well as improvement in the laboratory findings.[45, 49]

We prefer to consider all of the multiple tubular defects, including the idiopathic Fanconi syndrome, as being secondary manifestations of some disease process which inhibits or damages the proximal tubule. This attitude is maintained not to reject the possibility that an intrinsic tubular lesion may produce the Fanconi syndrome but to stimulate the search for other causes, in the hope that eventually some of these diseases can be corrected by removing the cause, rather than by treating the effect.

One other disease accompanied by dwarfism, which can be considered to be a proximal tubular dysfunction, is pseudohypoparathyroidism, although in this case the abnormality is an increase in reabsorption, rather than a decrease.[40]

Pseudohypoparathyroidism. This is a congenital disorder in which dwarfism, mental retardation, a typical facies, and short metacarpals are accompanied by the chemical changes of hypoparathyroidism. The low calcium and high phosphorus in the serum and low urinary excretion of phosphorus do not respond to parathyroid extract, and the defect is assumed to be an excessive reabsorption of phosphorus because of an inability of the proximal tubule to respond to endogenous parathyroid hormone.

The dwarfism and mental retardation accompanying this syndrome are not dependent on the renal defect, as they occur also in cases of pseudo-pseudohypoparathyroidism in which the serum calcium and phosphorus are normal and in which the tubular defect is apparently not present.[52]

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III. The distal nephron and disorders of its function

Malcolm A. Holliday, M.D.*

PITTSBURGH, PA.

THE DISTAL NEPHRON AND POLYURIA

THE RENAL tubules have many discrete functions which in summation modify glomerular filtrate to form urine. This includes reabsorption of salt and water to an extent that ensures a normal balance of salt and water, reabsorption of glucose, amino acids, and phosphate, acidification of the urine to excrete the usually acid ash residue of the diet, and regulation of potassium excretion to assure potassium balance. Much has been learned of various phases of these functions which, in many instances, are interrelated and interdependent. In considering the distal nephron alone it must be emphasized that many functions—acidification, sodium reabsorption, and potassium excretion—occur here to a limited extent. A most important function relegated to this area is the dilution and concentration of urine. It is this function that permits water excretion to increase or decrease independently. Failure of the concentration mechanism leads to the obligatory excretion of solute in more than the minimal volume of urinary water normally required, and polyuria results. It is permissible then from a clinical standpoint to discuss polyuria in terms of a disorder in function of the distal nephron. The interrelationship of this function to other tubular functions will become apparent.

The term distal nephron is used to include the tubule beyond the proximal convolution. It comprises the descending and ascending limbs of Henle's loop, the distal convolution, and the collecting system. The relation of these to gross kidney architecture is indicated in Fig. 1. Henle's loop and most of the collecting system are in the medulla, and the distal convolution and the beginning of the collecting system are in the cortex. Polyuria is defined here as the obligatory excretion of larger than normal volumes of urine so that minimum water requirements are increased. In mild instances the disorder may be apparent only on testing urine concentrating capacity; in severe instances the polyuria and accompanying polydipsia may be the major complaints. At least three different mechanisms can alter the function of the distal nephron so that polyuria results. The specific clinical disorders causing polyuria are diverse but these may be grouped under one of the three mechanisms as follows: (1) osmotic diuresis: diabetes mellitus, glycosuria of other causes, and chronic renal failure;

From the Department of Pediatrics, University of Pittsburgh School of Medicine, and the Heinz Memorial Laboratories at Children's Hospital.

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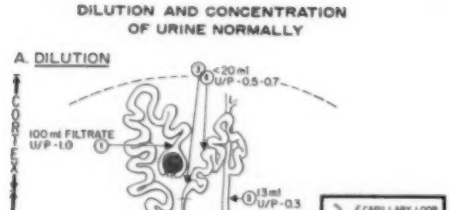
**Address, Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh 13, Pa.*



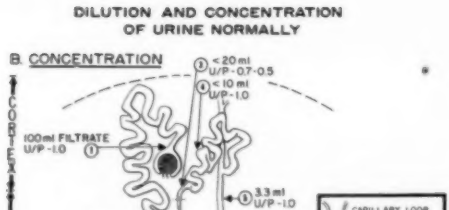


Fig. 1.

A. Dilution

1 to 2. 80 per cent water and solute removed in proximal convolution.
20 per cent filtered water and 20 per cent solute remain.

2 to 3. Little if any water is removed but half the remaining solute is removed.
18 to 20 per cent filtered water and 9 to 10 per cent filtered solute remain.

3 to 4. Nothing happens, fluid remains hypotonic.
18 to 20 per cent filtered water and 9 to 10 per cent filtered solute remain.

4 to 5. Reabsorption of salt continues. Some water reabsorption may occur but proportionately less than salt.
11 per cent filtered water and 3.3 per cent filtered solute remain.

5 to 6. Some additional salt is reabsorbed. Virtually no water is reabsorbed.
10 per cent filtered water and 1.7 per cent filtered solute is excreted.

B. Concentration

80 per cent and solute removed in proximal convolution.
20 per cent filtered water and 20 per cent solute remain.
Little if any water is removed but half the remaining solute is removed.

18 to 20 per cent filtered water and 9 to 10 per cent filtered solute remain.

Water leaves tubule until fluid becomes isotonic.
9 to 10 per cent filtered water and 9 to 10 per cent filtered solute remain.

Reabsorption of salt continues and water leaves passively so that tubular fluid remains isotonic.
3.3 per cent filtered water and 3.3 per cent filtered solute remain.
Some additional salt is removed. Water is reabsorbed to establish osmotic equilibrium with the interstitial fluid of the medulla. This is progressively hyperosmotic so that progressively more fluid is removed leaving behind a small volume of concentrated urine.
.5 per cent filtered water and 1.7 per cent filtered solute is excreted.

(2) disorders of the renal medulla: potassium deficiency, pyelonephritis, sickle cell disease, hypercalcemia, and acute tubular necrosis; and (3) failure of antidiuretic activity: psychogenic polydipsia, diabetes insipidus, and nephrogenic diabetes insipidus.

NORMAL URINE DILUTING AND CONCENTRATING PROCESSES

Before these disorders can be discussed in detail, the normal sequence of events concerned with the dilution and concentration of urine should be reviewed. The term dilute

urine refers to urine of total solute concentration (osmolar concentration) less than that of plasma or with a urine to plasma ratio (osmolar U/P ratio) of less than 1.0. The term isosmotic is used to describe urine equal to plasma in osmolar concentration (U/P ratio = 1.0) and the term concentrated urine is used to refer to urine of U/P ratio greater than 1.0. Table I compares specific gravity, osmolar concentration and U/P osmolar ratios for dilute urine, isosmotic urine in diabetes and in uremia, and concentrated urine of moderate and maximal degrees. The high specific gravity of diabetic urine contrasts with the lower osmolar concentration and is due to the high molecular weight of glucose. This discrepancy illustrates a limitation in the use of specific gravity to measure urine osmolar concentration.

Under circumstances where dilute urine is excreted, the dilution occurs by the reabsorption of a solute, principally sodium chloride, from tubular fluid without a corresponding reabsorption of water. The dilution of urine depends on the reabsorption of sodium chloride (an active process) in an area where water does not diffuse passively back with it. Under conditions where concentrated urine is excreted, the reabsorption of the solute occurs as above, but as the solute is reabsorbed, water passively diffuses with it so that less water is left behind in the tubule. The increase of solute concentration of urine to osmolar concentrations greater than plasma (U/P ratios greater than 1.0) is actually effected by passive diffusion of water from the collecting tubule into a hyperosmotic medulla. Concentration of urine depends on this area becoming more permeable to water so that the water can diffuse passively back into the hyperosmotic medulla. The development of a hyperosmotic medulla and a change in water permeability of tubular cells are essential requirements for this process.

A detail of the two processes is indicated in Fig. 1. The figures are drawn to represent a nephron excreting dilute urine (Fig. 1A) and concentrated urine (Fig. 2B) under usual circumstances of solute excretion (approximately 900 mOsm. per day). The volumes and the solute concentrations expressed as U/P ratios are indicated at 6 different sites along the nephron to indicate the sequence of events beginning with 100 ml. of isosmotic glomerular filtrate (300 mOsm. per liter or U/P ratio of 1.0). The key below the figure describes the changes between the numbered sites.

In both instances approximately 80 per cent of the filtered fluid is reabsorbed in the proximal convolution (Site 1 to Site 2) so that normally 20 per cent of the filtered fluid remains to be handled by the distal nephron. This remaining fluid is isosmotic (U/P of 1.0); glucose, amino acids, and most of the phosphate have been reabsorbed.[1] Little if any urea has been reabsorbed. The principal solute is still sodium chloride, although roughly 80 per cent of the filtered sodium chloride as well as 80 per cent of the water has been reabsorbed. It is believed that sodium is reabsorbed by active transport and that proportionately more bicarbonate than chloride follows it.[2] Water diffuses back passively. The active process then is reabsorption of sodium.

Dilution of urine. In the case of water diuresis (Fig. 1A) roughly half of the electrolyte, mostly sodium chloride, is removed in Henle's loop. Little if any water, however, is removed so that fluid leaving the loop is diluted to roughly half plasma solute concentration—U/P ratio 0.5 (Site 3). In the distal convolution this dilution is maintained as is symbolized by a sample at Site 4, which is the same as that at Site 3.[3, 4] However, sodium chloride reabsorption continues in the distal convolution with proportionately less water so that a large volume of dilute urine enters the collecting tubule (U/P ratio 0.3). As the fluid passes down through the collecting tubule (Site 5) reabsorption of sodium chloride continues with relatively less reabsorption of water.[5] The result is excretion of very dilute urine (Site 6). The outstanding feature of this system is the relative impermeability of the cells of the distal convolution and collecting system to

Table I

	Specific gravity	*Osmolar concentration (mOsm./L.)*	*U/P ratio*
Dilute urine (diabetes insipidus)	1.004	100	.20
Isosmotic urine (uremia)	1.010	240 to 360	.8 to 1.2
Isosmotic urine (diabetes mellitus)	1.040	240 to 360	.8 to 1.2
Moderately concentrated urine	1.020	500 to 700	1.6 to 2.4
Maximally concentrated urine	1.030	1200 to 1400	4.0 to 4.6

water such that as sodium chloride is removed a progressive osmotic gradient approaching one-fifth is developed between the tubular fluid and the surrounding fluid.* By this process a urine volume 5 times greater than that required to remove the same solute load at *isosmotic* concentrations can be excreted. The final volume of urine depends on the volume of urine entering Henle's loop and varies from 10 to 20 per cent of the filtered volume. This permits the rapid removal of excess ingested water. These events normally occur when no antidiuretic hormone is present in the circulation.

Concentration of urine. *Antidiuretic hormone.* The concentration of urine normally occurs in the presence of antidiuretic hormone† and this hormone appears to be principally responsible for the changes in processing of tubular fluid so that approximately the same solute is excreted, not as dilute urine or even isosmotic urine but rather as concentrated urine. Osmolar concentrations in man of 1200 to 1400 mOsm. per liter normally are observed in response to dehydration or vasopressin injection, corresponding to U/P ratios of 3.3 to 4.6. The volume of urine then is reduced by approximately one-fourth that required to excrete the same solute at isosmotic concentrations and one-twentieth or less than that utilized during water diuresis in the absence of any antidiuretic hormone. Vasopressin injection does not occasion quite as high a degree of urine concentration as does dehydration and natural antidiuretic hormone activity. Water deprivation itself has some conditioning effect.[7]

The countercurrent system. The process of concentration in the distal nephron (Fig. 1B) in the usual instance where 80 per cent of the filtrate that has been reabsorbed in the proximal convolution (Site 2) begins in Henle's loop where again proportionately more sodium chloride than water is reabsorbed. Fluid leaving the Loop (Site 3) is dilute like that described in the dilution process.[1] It is necessary at this stage to examine the mechanism of the reabsorption of sodium chloride in Henle's loop whereby half the sodium chloride and little if any water is removed. The interstitial fluid in the medulla is maintained at an osmolar concentration approaching 1400 mOsm. per liter. The osmolar concentration of the medulla increases from an isosmotic value at the corticomedullary junction to this high concentration as the tip of the papilla is approached. The development and maintenance of this gradient is dependent on the "hair-pin" configurations of Henle's loop and the vasa rectae. This configuration in which the inflow limb runs straight to the tip and then bends 180° so that the outflow limb runs adjacent

*Normally the extreme osmolar dilution in urine is 40 to 60 mOsm. per liter or a U/P ratio of 1/5 (0.2). We have observed an osmolar concentration of 12 mOsm. per liter in a child with nephrogenic diabetes insipidus or a U/P ratio approximating 1/25 (.04).

†All the effects of the posterior pituitary hormones can be accounted for by two principles which have been isolated in highly purified forms by du Vigneaud[8]: The antidiuretic-vasopressor principle, termed vasopressin, and the lactagogic-oxytocic principle, termed oxytocin. Both are octapeptides with similar structure. Virtually all the antidiuretic activity is due to vasopressin. It is used generally as a crude extract of the posterior pituitary with little oxytocic activity. The term antidiuretic hormone is used in this paper to describe the endogenous secretion of antidiuretic principle; the term vasopressin is used to refer to administered extract.

to it as it goes out is illustrated diagrammatically in Fig. 2. The *ascending limb,* or *outflow* tract, of Henle's loop actively pumps sodium chloride out of the fluid, some of which re-enters the corresponding segment of the descending limb. A small gradient is established between outflow and inflow such that outflow is relatively dilute and inflow relatively concentrated. As this process continues there is a progressive rise in solute concentration in both limbs, as forces attempting equilibrium across the limbs are countered by the pumping of salt from outflow to inflow. At no time is a steep gradient across the limbs established, but a progressive gradient toward the papillae is established (Fig. 2). This system is termed a countercurrent multiplier.

The vasa rectae are important in maintaining the system, for the plasma leaving the medulla must carry away the salt pumped out of the tubules once a steady state is reached, and yet permit the hyperosmolarity to remain. The entering capillary fluid is made progressively concentrated as it descends toward the papilla. On return the reverse process occurs but the capillary fluid "escapes" with the extra sodium. The rate of flow can vary the rate of sodium removal. This system is termed a countercurrent exchange system. The relative simplicity of this system is remarkable for it provides a highly efficient means of varying the rate of water excretion independent of solute excretion by a single substance, antidiuretic hormone, which has a single action: the change in tubule cell permeability to water.* Its conception we owe to Hargitay and Kuhn[3] and its demonstration we owe to the micropuncture studies of Wirz[3] and Gottschalk.[4]

Reabsorption of water. With this action of the antidiuretic hormone and the function of Henle's loop and the vasa rectae to establish the progressive osmolar gradient in the medulla the concentration of urine can be visualized simply. As indicated in Fig. 1B, the dilute urine leaving the loop (Site 3) and entering the distal convolution rapidly equilibrates with the surrounding isosmotic milieu, and in the process roughly half its volume is reabsorbed (Site 4). This is due to the effect of the antidiuretic hormone to increase the permeability of the cells of the distal convolution to water. Active reabsorption of sodium chloride continues and with it water passively leaves the tubules (Site 5). Thus not only solute but water is removed, whereas principally solute was removed during water diuresis. This process reduces the volume and to less extent the solute of the tubular fluid entering the collecting system. The reabsorption of solute continues in the collecting tubule,[5] but as the fluid passes down through the hyperosmotic medulla, water also leaves by passive diffusion. The water is removed from the medulla by the vasa rectae. Since the vasa rectae also remove

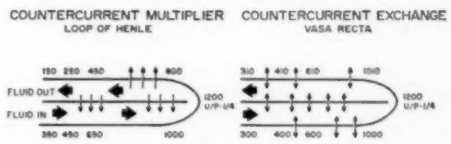


Fig. 2. The loop of Henle, a countercurrent multiplier. The countercurrent multiplier system of the loop of Henle is illustrated above. By pumping sodium chloride across from the *outflow* back into the inflow tract and by partial osmotic equilibration, a progressive gradient is established along the tubule. By pumping sodium chloride out of the tubule into the interstitium, the removal of sodium chloride from tubular fluid is effected. A gradient across the tubules of approximately 200 mOsm. per liter is believed to exist.[4] The vertical gradient toward the papilla is much higher.

The vasa recta, a countercurrent exchanger. The vasa rectae are not believed to actively pump sodium chloride. As the fluid approaches the tip it becomes progressively concentrated. As it leaves it returns toward its incoming concentration. By leaving with a slightly higher concentration of sodium chloride than it had on entering, however, it can remove the sodium chloride pumped out of tubular fluid. In this way the papilla stays in sodium chloride balance.

***The antidiuretic hormone itself may affect directly the transport of sodium chloride and urea. Furthermore, the change in flow rates themselves have some effect. Nonetheless, under ordinary circumstances, the effects of the antidiuretic hormone other than those attributable to changes in water permeability probably are slight.**

the proportionately greater quantities of sodium chloride pumped out by Henle's loop, the proper requirements for maintaining the hyperosmolarity of the medulla exist. The excretion of a small volume of concentrated urine is thus effected (Site 6).

The outstanding feature of this system is the fact that the medulla is the site of more removal of sodium chloride than removal of water, whereas the distal convolution in the cortex and the collecting tubule in the medulla effect a greater removal of water than of salt. The former is made possible by the countercurrent systems described and the latter by the fact that the distal convolution and collecting tubule are made more permeable to water by the antidiuretic hormone. The efficiency of the concentrating system in the collecting tubule depends on (a) the rate of removal of salt by Henle's loop in excess of the removal of water, (b) the removal of corresponding amounts of water in the distal convolution in the cortex, and (c) the removal of relatively small amounts of water from the collecting tubule in the medulla to concentrate urine. The concentration of urine in the collecting tubule to osmolar levels above plasma levels depends upon the prior dilution of urine in Henle's loop.

CLINICAL DISORDERS CAUSING POLYURIA

It was cited at the beginning that polyuria can result from any of three mechanisms: (1) osmotic diuresis, (2) disorders of the renal medulla, and (3) failure of antidiuretic activity. The remainder of this section will concern itself with a description of clinical examples of each of these conditions. In some instances, notably uremia, potassium deficiency, and diabetes insipidus, recent experimental information is reviewed.

Osmotic diuresis. *Diabetes mellitus.* The polyuria of osmotic diuresis results from the filtration of solute which is incompletely absorbed. In the case of glucose in diabetes mellitus the amount filtered is greatly increased over normal, and the normal reabsorptive capacity of the proximal convolution (glucose Tm) is exceeded. The remaining glucose is consequently delivered into the distal nephron where no reabsorption is believed to occur. The osmotic effect of this solution limits the back diffusion of water in the proximal convolution, so, consequently, more fluid is also delivered to the distal nephron. In addition, less salt is reabsorbed, possibly as a consequence of the more rapid flow rates and larger volumes of fluid in the tubule. Accordingly, the capacity of Henle's loop to extract sodium is exceeded and the opportunity for maximal passive water reabsorption to occur in the distal convolution and collecting tubule is diminished. The end result is the excretion of more solute including more sodium chloride in a larger volume of water than occurs normally. In diabetes the filtration rate is normal, and the total volume of fluid delivered to the distal nephrons is high. There is an increase in the volume of urine which may reach 10 to 20 per cent of the filtered volume. In experimental osmotic diuresis, e.g., infusion of mannitol, rates of excretion equal to 30 to 40 per cent of the filtered volume have been observed. A simple example may clarify: if in diabetes mellitus, the filtration rate is 100 ml. per minute and instead of 20 ml. fluid delivered to the distal nephrons 35 ml. is delivered, the urine volume could increase from 1 ml. per minute (1 per cent filtered volume) to 16 ml. per minute (16 per cent filtered volume) without supposing any change in distal nephron function.

Chronic renal failure. The uremia of chronic renal failure implies a great reduction in the number of functioning nephrons and a great reduction in the total filtered volume. The reduction in total filtered volume results in a corresponding increase in concentration of urea, and almost certainly in a compensatory increase in the volume of filtered fluid for each remaining functional nephron. Three features are important. (1) The total volume of filtered fluid is decreased so that the volume of fluid to be modified, and the number of nephrons to modify it, are decreased. Thus if filtration were 10 per cent of normal and all else were equal, one

would expect the maximum rate of water excretion in water diuresis to be diminished to 10 per cent. A similar absolute change in water conservation, i.e., the rate at which the kidney can extract water from isosmotic urine, would be observed. However, if the rates of these functions per 100 ml. filtration rate were normal, (2) the reduction in the over-all filtration rate does result in an elevation in the concentration of plasma urea so that a solute diuresis due to urea would result, and (3) the destruction of a number of nephrons would almost certainly result in a considerable increase in the volume of filtered fluid in each of the remaining nephrons. This change results in an osmotic diuresis due to sodium chloride. These latter two factors combine to impose on the functioning distal nephron the same limitations that the glucose diuresis occasioned in diabetes mellitus.

A fourth factor only recently has been isolated successfully and, in fact, found to play a minor role. This is the question as to whether the remaining nephrons are capable of normal tubular function or whether tubular function per se is altered by the diffuse renal disease. The problem was studied recently in dogs, in which one kidney was diffusely damaged by either nephrotoxic serum, aminonucleoside injection, or infection; the other kidney was not injured. Plasma concentration of urea and electrolyte remained at normal values. The capacity of the damaged kidney to concentrate urine was nearly normal and the rate of "free" water excretion per 100 ml. filtrate during water diuresis and the rate of water extraction during osmotic diuresis in terms of 100 ml. of filtered fluid were near normal.[9] It appears that the limitations to concentrate and dilute urine in uremia may be the result of the osmotic diuresis natural to that state rather than of an intrinsic disorder of the distal nephron itself.

The characteristics of the polyuria of uremia are well known. The volume of urine is modestly increased from one- to twofold and the specific gravity is "fixed," with the solute concentration being very nearly that of plasma, i.e., U/P ratio of about 1.0, with little change in response to the ingestion or deprivation of water. The individuals lack the capacity for concentration of urine at night so that nocturia is commonly observed. The total volume of urine may represent 20 to 40 per cent of the volume of the glomerular filtrate, but since the latter is very low, the urine volume is not great. For example, if the filtration rate is 7 ml. per minute and urine flow is 2 ml. per minute, urine flow is 29 per cent of filtration rate but only 2 to 4 times the usual flow.

When the filtration rate is much below 30 per cent of normal, polyuria becomes clinically manifest. It is self-evident that at this time, the capacities to concentrate and dilute urine are predictably diminished and some hazards attend the tests used to measure such functions. In lesser degrees of renal damage when plasma urea is near normal, the above tests may be sensitive indices, but unless a differentiation is sought between diffuse renal disease and one of the specific states noted below, it is of little value.

Disorders of the renal medulla. *Potassium deficiency.* In recent years it has been established that individuals with demonstrable potassium deficiency have a diminished ability to concentrate urine.[10] The observation has been noted experimentally in rats.[11] In the latter, fairly extensive studies have been carried out which, in effect, show that complete restoration of function is possible after a deficiency of 3 to 4 weeks,[12] but some permanent impairment is observed after 3 months of deficiency.[13] It has been shown also that the capacity to dilute urine or to excrete water is not impaired to a corresponding degree.[14]

Morphologically, lesions in the collecting tubule of rats have been described, whereas Henle's loop appears normal.[15] Similar findings in humans are difficult to verify because this area frequently is not examined. Nonetheless, the good correlation between the lesions in experimental rats and the concentrating defect in both humans and rats do suggest a relationship. The finding of normal water excretion and free water clearance

corresponds to the morphologically normal Henle's loops. These observations suggest that the dilution of urine in Henle's loop is adequate, but that the final concentration is impaired in potassium deficiency either because there is a change in tubular permeability to water or because there is a diminished osmolarity of the medulla.

Potassium deficiency of long standing is a rare disease in any age group, but particularly in children. Its occurrence generally has been in patients with aldosteronism, chronic diarrhea from ingestion of laxatives, pyloric stenosis or postoperative surgical patients with persisting intestinal losses. With the exception of pyloric stenosis in infants, none of these are common in the pediatric age group. It has been proposed that the polyuria characteristic of the de Toni-Fanconi syndrome is due to a chronic potassium deficiency. Evidence for the existence of potassium deficiency in this state is indirect; hypokalemia is a fairly consistent finding and the excretion of potassium in urine is high and is reversed by sodium administration in a manner analogous to that seen in other forms of renal tubular acidosis with documented potassium deficiency. Balance data also lend support to this concept.[16] There are many other renal lesions, however, and no studies of urinary concentration in these patients before and after potassium deficiency have been reported in detail.

Clinically, humans with potassium deficiency do not necessarily have alkalosis. Renal lesions in humans have been described as hyperplasia of the convoluted tubules. However, the exact location of the hyperplasia is not established. The urine concentrates to specific gravities of 1.012 to 1.015 or to a U/P ratio only slightly in excess of 1.0 in response to deprivation of water or administration of vasopressin.[10] The capacity to excrete a water load does not seem impaired. It is not clear that the observed polydipsia and polyuria are entirely explained by this defect. The intake of water seems greater than that required by the limit in concentrating capacity. This may be a simple function of conditioning, or it may reflect a direct effect of potassium deficiency on the thirst mechanism. A similar defect has been noted in hypercalcemia and vitamin D intoxication.[17, 18]

Pyelonephritis. It is well established that pyelonephritis can produce uremia and consequently, in this instance, polyuria due to uremia is observed. Recently, in experimental pyelonephritis, a defect in the urine concentrating capacity was observed without uremia.[19] Lesions in the medulla were prominent. It is too early to correlate this observation to human experience, but tests of concentrating capacity and studies of glomerular filtration, i.e., urea or creatinine clearance are clearly indicated. It may develop that the former is a more sensitive index of medullary disease in pyelonephritis and, consequently, a better index of renal disorder in certain forms of pyelonephritis than is a clearance study.

Sickle cell disease. This remarkable disease has its effect on every organ and physiologic system in the body. Even its "asymptomatic" carrier state (sickle cell trait) is accompanied by measureable changes in function. In the individuals with the trait and with the disease, a degree of polyuria is present though usually detected only on testing concentrating capacity.[20] This defect appears in the absence of anemia or other signs of renal dysfunction. In young children it is reversed by replacement transfusion of normal cells for the sickle cells.[21] There are studies, however, which describe normal excretion and normal conservation of water in these children during osmotic diuresis and which suggest the possibility that water deprivation might increase the sickling phenomenon and thereby alter the blood flow, particularly in the vasa recta.[22]

It is curious that over 20 instances of bleeding from the renal papillae have been reported in patients with sickle cell *trait,* nephrectomy being required frequently because of severe bleeding. Pathologic reports of such kidneys describe changes in glomeruli and in the tubules of the medulla, the latter being more evident. Some of the changes might reflect acute sickling incident to the anoxia that attends the removal of such

kidneys.[23] The evidence is nontheless convincing that morphologic disruption of the medulla of the kidney again correlates with a defect in concentrating capacity of the kidney, although the mechanism is not defined.

Acute tubular necrosis. A period of diuresis often ensues following anuria due to acute tubular necrosis. This may be a diuresis of isosmotic urine in which the mechanism for electrolyte reabsorption is impaired. Swann and Merrill[24] have cited the fact that some of the diuresis is due to accumulated edema fluid. They have demonstrated that individuals in this phase do have some response to water loads and to salt loads, although both are blunted. The capacity to concentrate urine is limited. There is damage in the proximal convolution and throughout the distal nephron and functional evidence of the effect of diffuse tubular damage on electrolyte reabsorption.

Disorders of the antidiuretic system. It has been noted already that even when concentrated urine is excreted, the fluid leaving Henle's loop is hypotonic. When there is no antidiuretic hormone, this fluid remains dilute and becomes even more so as it passes through the distal convolution and collecting tubule. Normally this occurs only transiently in response to excess ingestion of water. Injection of vasopressin during water diuresis, even in large amounts, does not result in a concentrated urine as does the combination of dehydration and antidiuretic activity. The continued ingestion of water results in considerable limitation in concentration of urine.[25] Three clinical disorders result in excretion of abnormally dilute urine with no significant increase in solute excretion, i.e., polyuria characteristic of water diuresis. They are psychogenic polydipsa or the compulsive ingestion of water, diabetes insipidus in which production of the antidiuretic hormone is deficient or absent, and congenital vasopressin-resistant diabetes insipidus in which response to antidiuretic hormone or administered vasopressin does not affect concentration of urine.

Psychogenic polydipsia. This disorder is seen in the pediatric age group as an expression of an emotional disturbance. It is included in this group for two reasons. It may be sufficiently severe to mimic diabetes insipidus, and it recently has been demonstrated that these individuals,[26] as well as volunteers drinking excess water,[25] lose their capacity to concentrate urine to less than normal U/P ratios (1.0 to 2.0). With cessation of excessive drinking of water, the capacity to concentrate urine normally does return. This observation throws some light on the normal events during water diuresis, for it is self-evident that the capacity to dilute urine is not limited, and consequently the removal of sodium chloride from Henle's loop continues efficiently. The difficulty must lie either in some dissipation of the hyperosmotic milieu in the medulla or in rendering the membrane of the distal convolution and collecting tubule less responsive to antidiuretic hormone.

In patients with psychogenic polydipsia the posterior pituitary system is intact. This can be demonstrated by the Hickey-Hare test[27] which consists of the infusion of hypertonic sodium chloride solution (6 to 8 ml. of 5 per cent solution per kilogram) given over 20 to 30 minutes to the subject during active water diuresis. If the posterior pituitary is intact, an increase in serum osmolarity stimulates the excretion of ADH, and urine flow consequently decreases. Concentration of any of the solutes of urine, e.g., sodium chloride or urea, or of total solute concentration, will increase correspondingly.[27, 28] The effect of hypertonic saline to stimulate secretion of the antidiuretic hormone was first described by Verney[29] who injected hypertonic sodium chloride solution into the carotid artery of dogs during water diuresis and demonstrated prompt antidiuresis. A normal response is illustrated in Fig. 3, *A*. A person with psychogenicpolydipsia has a qualitatively similar response, although its degree, as noted above, may be less.

The treatment of the condition is ultimately dependent on a resolution of the emotional disorder. Programs of enforced

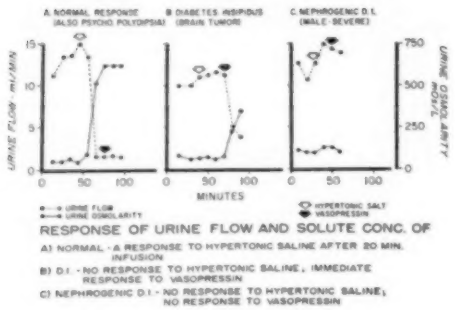

A. NORMAL RESPONSE (ALSO PSYCHO. POLYDIPSIA)
B. DIABETES INSIPIDUS (BRAIN TUMOR)
C. NEPHROGENIC D.I. (MALE - SEVERE)
URINE FLOW - ML/MIN
URINE OSMOLARITY MOS/L
MINUTES
URINE FLOW
URINE OSMOLARITY
HYPERTONIC SALT
VASOPRESSIN
RESPONSE OF URINE FLOW AND SOLUTE CONC. OF
A) NORMAL - A RESPONSE TO HYPERTONIC SALINE AFTER 20 MIN. INFUSION
B) D.I. - NO RESPONSE TO HYPERTONIC SALINE, IMMEDIATE RESPONSE TO VASOPRESSIN
C) NEPHROGENIC D.I. - NO RESPONSE TO HYPERTONIC SALINE, NO RESPONSE TO VASOPRESSIN

Fig. 3.

water restriction are ill advised. Administration of vasopressin therapeutically may likewise be serious as the individuals may continue with the compulsive ingestion of water and develop water intoxication. It is fair to point out that, as in all behavior disorders, the clinical manifestation may clear without basic improvement in the emotional structure.

Diabetes insipidus. Like psychogenic polydipsia, diabetes insipidus is not a disease of the tubule per se. It occurs when there is a relative or absolute deficiency in production of the antidiuretic hormone. Accordingly, the stimuli normally resulting in its release and action upon the distal nephron are ineffectual. Dilute urine continues to be excreted and this requires ingestion of large amounts of water to replace the losses. The urine has the characteristics of that described during water diuresis, i.e., solute concentration of less than 100 mOsm. per liter (U/P ratio 0.3). The volume of urine is 3 to 6 times that required to excrete the same solute load at 300 mOsm. per liter (U/P ratio 1.0), as in chronic uremia, and is 12 to 20 times that required to excrete the solute load at maximum concentration (1200 mOsm. per liter; U/P ratio 4.0).

The condition is relatively rare. It is observed in association with brain tumors, in Hand-Schüller-Christian disease, in vascular disease of the central nervous system, and spontaneously without specific cause. The signs of diabetes insipidus per se are polyuria and polydipsia. Diagnosis is generally evident from the history and from the character and volume of urine excreted. It is established by the absence of a response to the administration of hypertonic saline, and by a sharp decrease in urine flow in response to intravenous or intramuscular aqueous vasopressin (Fig. 3, *B*).

With water deprivation the urine flow continues until a water deficiency develops resulting in an increase in solute concentration in the body fluids (indicated by an increase in serum sodium concentration). As this progresses, renal blood flow and the glomerular filtration rate decrease with a consequent decrease in urine flow. The reduction in urine flow in this circumstance is accompanied by an increase in urine concentration, even though no antidiuretic hormone is available. This sequence of events was confirmed in experiments in dogs. Urine was collected separately from each kidney of dogs during water diuresis (no ADH). The filtration rate was reduced in one kidney by partial occlusion of the renal artery. Urine flow in that kidney greatly decreased and urine osmolar concentration rose to values above plasma. Urine from the unaffected kidney remained dilute.[30] This establishes the fact that a small amount of water diffuses back from the tubular fluid in the distal nephron in the absence of antidiuretic hormone, but this is not apparent until the total volume of fluid in the tubule is greatly decreased. This constitutes further argument that the principal action of this hormone is simply to increase the rate of diffusion of water. Clinically it indicates that excretion of concentrated urine in diabetes insipidus is possible with extreme reduction in the filtration rate due to a decrease in renal blood flow. Clinically the demonstration of urine concentration by water deprivation is extremely uncomfortable and unnecessary. For the reasons cited above, if it is done, changes in body weight and concentrations of serum sodium should be observed. Excretion of concentrated urine in the absence of unusual changes in either is indicative of a

normal antidiuretic response. The injection of vasopressin leads to a prompt increase in urine osmolar concentration to levels of 400 to 600 mOsm. per liter (U/P ratios of 1.3 to 2.0). It is known that despite administration of maximum doses of vasopressin, the U/P ratio is not as high as that observed with dehydration. Furthermore, with continued administration of the hormone and establishment of lower excretory rates of water maximal response to a dose increases. This is analogous to the experience noted with voluntary drinking of water and psychogenic polydipsia.

Vasopressin can be given either as an aqueous solution, a powder which may be insufflated into the nose, or a suspension in oil. The aqueous solution has to be injected and its period of action is only 4 to 6 hours. The nasal powder is quite effective in children old enough to use the insufflator, the amount varying between 20 to 40 mg. given 2 to 4 times daily as dictated by the symptom of polyuria. Some children and adults experience sufficient nasal irritation so that it cannot be used in this way. Others cannot cooperate. In such instances the use of vasopressin in oil is indicated. It has the disadvantage of being expensive, being difficult to mix, and requiring deep intramuscular injection. From 2 to 5 units every 2 to 3 days are required to control symptoms. Replacement therapy effectively takes care of the symptoms due to antidiuretic hormone deficiency per se.

Nephrogenic diabetes insipidus. This disorder is an hereditary disease resembling diabetes insipidus in all ways except that replacement therapy with antidiuretic hormone is not effective. It is present at birth; it varies greatly in severity; some infants develop symptoms in the neonatal period, whereas others are minimally symptomatic throughout life. Males are affected more severely than females. The genetic pattern is not settled; more than one pattern may exist. It appears to be a dominant trait that may be autosomal or may be sex linked with variable penetrance.[31, 32, 33] When it is severe, the symptoms in infancy are not so much polyuria per se and polydipsia, but rather symptoms of water deficits or dehydration. An infant depending on offered milk and water for his intake of water often cannot indicate his thirst. In such infants, who are almost invariably males, the symptoms are nonspecific, consisting of failure to thrive, loss of weight, and malaise. Fever with hypernatremia and constipation are more specific signs of dehydration. Brain damage often occurs in these infants as a result of dehydration and hypernatremia. The common association of mental deficiency with this disorder can be explained on this basis, although it is not the only cause, since a congenital brain defect may coexist or may cause pituitary diabetes insipidus. Beyond childhood, lesser degrees of polyuria and polydipsia are the only symptoms. These symptoms are commonly noted in the female carrier, especially in mothers of affected infants.[32, 33]

The nature of this disorder is not established. The failure to respond normally to an administered antidiuretic hormone can be visualized as either a defect in the kidney or in the pituitary system. In the former case it is presumed that the membrane lining of the distal nephron is chemically altered so that the normal antidiuretic hormone is not effective either in attaching to the kidney or in affecting its action once it is attached. No histologic abnormalities have been found in the material studied at autopsy.[34] No other functional disorder has been noted with any consistency in association with this defect.[32, 34, 35] Neither of these negative observations are inconsistent with the above supposition, however. Should the pituitary fail to produce antidiuretic hormone it might be argued that response to an administered hormone has to be conditioned analogous to the circumstance seen after ingestion of water. Antidiuretic activity has been reported in urine[35] and in serum[34] of dehydrated subjects with this disease; on the other hand, blood from these patients appeared to block antidiuretic response of vasopressin, when the vasopressin was mixed with the blood and injected into

normal subjects.[31] The data presented are insufficient to establish that these individuals secrete normal antidiuretic hormone. It is possible that they may secrete an abnormal hormone which fixes on the kidney receptor site. Lacking antidiuretic activity, it may block the action of the normal antidiuretic hormone. Recently we have observed an improvement in response to an administered antidiuretic hormone in a child with nephrogenic diabetes insipidus when the hormone was given over a period of 1 month. The data are too limited to constitute anything more than a stimulus for further study.

The mechanism in the tubular handling of fluid like that in diabetes insipidus, is identical to normal diuresis of water. However, neither normal stimuli to antidiuretic hormone secretion nor to administration of vasopressin results in concentration of urine. In very severe cases *no* change in osmolar concentration occurs with vasopressin administration (Fig. 3, *C*). In less severe cases the response is less than normal.

One male infant and one 6-year-old boy (Fig. 3, *C*) studied here showed no renal response to 100 mU of vasopressin administered intravenously. Urinary osmolar concentration did not change. A decrease in urinary flow was noted in the infant in response to vasopressin. His daily osmolar excretion was reduced by low protein feedings to very low levels, 8 mOsm. per kilogram per day (usually 15 to 40 depending on protein intake). At this point his urine was extremely dilute (12 mOsm. per liter) but his maximum rate of water excretion was actually low, approximately half of the normal. By inducing a mild osmotic diuresis with glucose his rate of water excretion returned to normal. This may be an effect of the extremely low rate of solute excretion in the first period.

His mother experienced polyuria and polydipsia throughout childhood and had a reappearance of these symptoms during pregnancy. She always "felt thirsty." Her response to overnight water deprivation was below normal (650 mOsm. per liter). She had nearly as good a response to vasopressin administered intravenously. Vasopressin by insufflation produced relief of all her symptoms.

Most recently chlorothiazide has been used in patients with diabetes insipidus and nephrogenic diabetes insipidus.[36] Considerable relief of symptoms and improvement in capacity to concentrate urine has been noted.

There remain several unanswered questions. For example why is the response to vasopressin less than that to dehydration and vasopressin? Why does persistent excessive ingestion of water limit concentration of urine? Why can antidiuresis in females with the "vasopressin-resistant" diabetes insipidus be interrupted when there is complete unresponsiveness in affected males? Why is chlorothiazide effective?

The treatment is not defined well. Experience with chlorothiazide justifies its use, although some failures have been noted. Continuous administration of vasopressin may be beneficial. Provision for a sufficient intake of water is essential. Efforts to reduce solute excretion by low protein diets are not always satisfactory. Early detection is essential, for it is during this period that dehydration, hypernatremia, and brain damage from them occur.

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Immunizing properties of live attenuated measles virus

Joseph Dolgin, M.D.,* Seymour Levine, Ph.D., F. S. Markham, Ph.D., Victor Cabasso, Sc.D., Manfred Weichsel, M.D., J. M. Ruegsegger, M.D., and Herald R. Cox, Sc.D.

STATEN ISLAND, N. Y., AND PEARL RIVER, N. Y.

AN EFFECTIVE immunizing procedure against measles is urgently needed and would be of tremendous value. Measles is one of the most serious of the common diseases of childhood. Our efforts to date have been directed largely toward combating secondary infections that follow in its wake. The antibiotics have played a significant role in diminishing the severity of these complications. In spite of all efforts, however, considerable mortality still occurs as a result of measles: 490 deaths were attributed to measles in the United States during 1958.[1] Staphylococcal pneumonia which may occur as a complication of measles results in a high mortality rate and is often resistant to antibiotic treatment. Measles encephalitis[2] remains a dreaded illness with considerable mortality or permanent disability. The effects, if any, of measles on the developing fetus in the early months of pregnancy need further investigation.[3]

Progress in measles prophylaxis had been greatly delayed for many years because of the absence of a simple technique for detecting virus multiplication. Shaffer, Rake, Stokes, and O'Neil[4] in 1941 propagated what was believed to be the measles virus in the chick embryo, but they were unable to demonstrate any cytopathogenic effects in the embryonic tissue. Material that had undergone serial chick embryo passage was then inoculated into monkeys and children. Mild but definite measles is reported to have occurred in several of the children as well as in the monkeys. The results on the whole were, however, inconclusive and suffered from the lack of an available method for demonstrating infectivity, viral multiplication, and antibodies.

This obstacle was finally removed in 1954 when Enders and Peebles[5] were successful in demonstrating cytopathogenic effects of the measles virus in tissue culture. They also demonstrated that antibodies developed in the serum of patients recovered from measles could be measured by the ability to prevent these cytopathogenic effects. This fundamental contribution made available the tools for studying the effects of the measles virus in man on a scientific basis. One additional difficulty, however, still remained. Enders[6] and others have pointed out that human cells may carry the risk of introducing latent viruses potentially path-

From the Division of Pediatrics of the Sea View Hospital, Staten Island, N. Y., and the Virus and Rickettsial Research Division of the Lederle Laboratories, Pearl River, N. Y.

**Address, 33 Central Avenue, St. George, Staten Island 1, N. Y.*

ogenic for man and therefore would be hazardous if used in the preparation of a vaccine. The proteins of the chick embryo, however, are well tolerated by humans, as is proved by the large scale use of yellow fever and influenza vaccines. After Enders and Peebles demonstrated propagation of the measles virus in primate cells by the tissue culture technique, it was not long before it became possible to demonstrate propagation of the measles virus in chick embryo tissue culture.[7]

METHODS AND MATERIALS

Patients and route of vaccine administration. The patients in this study consisted of children in the pediatric division of Sea View Hospital, an institution for the care and treatment of tuberculosis. Children selected for the study were those whose disease processes were stabilized and controlled. The vaccine was administered by the subcutaneous route.

Virus strains. The Edmonston strain of measles virus was used. It was received as the thirteenth passage in chick embryo tissue culture. Two different passage series were developed from this virus preparation. In one series the virus was passed twice in tissue culture monolayers of chick embryo lung followed by consecutive passages in the amniotic sac of the embryonated chicken egg. In the second series the virus was passed 3 times in chick embryo tissue culture, once in monkey kidney tissue culture, and finally back into chick embryo tissue culture. The vaccines used consisted of (a) Lot No. 7-1236-13, the fifth passage in the amniotic sac of the embryonated egg, and (b) Lot No. 7-1236-14, a chick embryo tissue culture passage.

Tests for bacteria and for extraneous viruses such as herpes, B virus, lymphocytic choriomeningitis, Coxsackie, etc., were negative on samples of both lots of vaccine.

Virus assay. Both virus preparations were titrated in monolayers of Hela cells.[8]

Antibody assays. The antibody content of all sera collected before and after vaccination was determined by the virus neutralization test. Serial twofold dilutions of serum were mixed with approximately 100 tissue culture infective doses ($TCID_{50}$) of measles virus and incubated for 1 hour at room temperature. The serum-virus mixtures were then inoculated in 0.1 ml. amounts into each of 2 Hela cell tissue cultures. The cultures were incubated at 37° C. and examined for evidence of cytopathology at regular intervals for a period of 2 weeks. An antibody free serum, a known immune serum, and a titration of the test virus were included as controls in each test. The serum neutralization titers were calculated by the method of Reed and Meunch.[9]

RESULTS

Study A: To determine the response to the vaccines. A random sample of 20 children who, because of their age, might not yet have had measles was selected. Blood was drawn from each child by venipuncture for antibody determination; each child was then tested for egg sensitivity by the intradermal injection of one minim of influenza vaccine (Lederle). The skin test proved negative in all the children. Five of the children were then immediately given 1 ml. of vaccine prepared in the amniotic sac. This was subcutaneously injected and calculated to contain 6,000 $TCID_{50}$. An additional 5 children were given 0.5 ml. of the same material. The remaining 10 children were given the chick embryo tissue culture vaccine which contained 100 $TCID_{50}$ per ml. Five children were each given 1 ml. and the remaining 5 were given 0.5 ml. of the same preparation. Nasopharyngeal swabs were taken from each child on the seventh, ninth, and eleventh day after vaccination. These swabs were then implanted on monolayers of Hela cells in an attempt to recover the virus. A repeat venipuncture was again performed on each child on the twenty-fifth day after inoculation for neutralizing antibody determination.

Eleven children in this group of 20 were considered susceptible to measles because of the absence of neutralizing antibodies in their sera. All 11 of these children had a

significant titer of neutralizing antibodies 25 days after the inoculation of attenuated live measles virus. Table I summarizes the antibody determinations in all 20 children. Of the 11 children whose antibody titers were less than 1:4 and who were therefore assumed to be susceptible, 6 received the amniotic sac passage vaccine and the remaining 5 the tissue culture vaccine. The 5 susceptible children who received the tissue culture material remained completely asymptomatic except for one child who developed a fever of 103° F. on the eighth day after his injection. Examination revealed an acute suppurative tonsillitis. He had a leukocytosis of 16,000 and a throat culture revealed a hemolytic staphylococcus. There were no clinical findings suggestive of measles in this child. In the 6 children who received the amniotic sac vaccine a febrile response occurred. It lasted from 2 to 4 days and generally ranged from 101 to 103° F., although occasional temperature recordings were even higher. The incubation period ranged from 5 to 8 days, as judged from the moment of inoculation of measles virus until the first evidence of fever or skin eruption, whichever appeared first. A faint maculopapular rash was observed in 4 of these 6 children. This involved the face and occasionally the chest, abdomen, and extremities. The eruption disappeared quickly, only lasting for a day or 2 or even less. Unequivocal Koplik spots were not recognized in any of these children. All of these 6 children showed a leukopenia and a relative lymphocytosis. None of these 6 showed any of the catarrhal symptoms, such as cough, coryza, or conjunctivitis, associated with naturally acquired measles. None of these children appeared toxic or acutely ill even where the temperature was significantly elevated. Thus the clinical picture in this group who received the amniotic sac material was very similar to modified measles after the use of gamma globulin. However, the incubation period was shorter than that which occurs when measles is modified with gamma globulin. In no case were pyogenic complications encountered. Table II gives a summary of the clinical manifestations in this group. We were unable to recover the measles virus from the nasopharyngeal swabs of any of the children in the group.

Table I. Virus neutralization titers of sera of children vaccinated with Edmonston strain of virus

Vaccine	*Dose*	*Child*	*Antibody titers**	
			Pre	*Post*
Amniotic sac	0.5 ml.	1	177	89
		2	< 4	128
		3	< 4	177
		4	< 4	89
		5	708	512
	1.0 ml.	6	128	177
		7	< 4	354
		8	< 4	256
		9	< 4	256
		10	4	22
Chick embryo tissue culture	0.5 ml.	11	< 4	22
		12	32	44
		13	89	64
		14	< 4	89
		15	< 4	64
	1.0 ml.	16	32	48
		17	512	1024
		18	< 4	16
		19	< 4	44
		20	708	708

*This represents the reciprocal of the end point dilution.

Study B: To determine the relationship of dose to clinical and serologic response. The second part of the study was carried out only with amniotic sac vaccine. This was a quantitative study with varying dilutions of vaccine in order to investigate the relationship of dosage to clinical manifestations and antibody response. Blood was drawn by venipuncture from 40 additional children for preliminary screening for measles antibodies. This group included 4 children from the private pediatric practice of one of us (J. D.). Ten children of this group were considered susceptible to measles as indicated by the absence of neutralizing antibodies. Immediately prior to inoculating these children with dilutions of the amniotic sac vaccine, venipuncture for antibody de-

Table II. Summary of clinical manifestations of first group who received live attenuated measles virus grown on the amniotic sac of the chick embryo

Case No.	*Age and race*	*Fever duration and range*	*Incubation period*	*Skin eruption and Koplik spots*	*WBC and differential*	*Catarrhal symptoms and toxicity*
1	3 years White	4 days 100.4 to 102°	5 days	Faint maculopapular rash over face; Koplik spots absent	6,500 polymorphonuclear leukocytes 32, all segmented; lymphocytes 68	Absent
2	2 years Negro	2 days 100 to 102°	8 days	A few maculopapules were noted on face; Koplik spots absent	6,600 polymorphonuclear leukocytes 30, all segmented; lymphocytes 68; monocytes 1; eosinophil 1	Absent
3	2 years Negro	3 days 101.2 to 104.2°	6 days	Faint maculopapular rash over face; Koplik spots absent	6,800 polymorphonuclear leukocytes 46; 2 staffs; 2 myelocytes; small lymphocytes 48; monocytes 6	Absent
4	20 months Negro	2 days 100.4 to 104°	7 days	No rash; Koplik spots absent	6,750 polymorphonuclear leukocytes 42, all segmented; lymphocytes 50; monocytes 8	Absent
5	2½ years Puerto Rican	1 day 101.8 to 103°	8 days	No rash; Koplik spots absent	5,800 polymorphonuclear leukocytes 28, all segmented; lymphocytes 72	Absent
6	2 years White	2 days 101 to 102.6°	8 days	Faint maculopapular rash over face, chest, and back; Koplik spots absent	5,650 polymorphonuclear leukocytes 20, 18 segmented and 2 staffs; lymphocytes 78; monocytes 2	Absent

termination was again performed to eliminate the possibility of inapparent infection or missed disease in the interval. Two of the children were given 1 ml. each of undiluted vaccine containing 6,000 $TCID_{50}$ per ml.; 2 were given 1 ml. each of a $\frac{1}{10}$ dilution of this material; 3 were each given 1 ml. of a $\frac{1}{100}$ dilution, and the remaining 3 were given 1 ml. each of a $\frac{1}{1000}$ dilution. Venipuncture for neutralizing antibody determination was performed on the twenty-ninth day after inoculation.

Table III summarizes the results of the virus neutralization tests with sera from 10 susceptible children in this group. Each susceptible child developed a significant titer of neutralizing antibodies after vaccination. The clinical course in these children was essentially similar to that of the first group who received undiluted amniotic sac virus. Two children, however, showed no symptoms. One of these had been given the undiluted material, 6,000 $TCID_{50}$, and the other received a $\frac{1}{10}$ dilution. A faint and transient maculopapular rash over the face, chest, and occasionally the abdomen occurred in 4 cases. A febrile response was noted in 8 cases and was similar in duration and degree to the first group. The blood was examined in 4 of the children who were febrile and revealed a leukopenia and a relative lymphocytosis in each case. The incubation period ranged from 5 to 13 days. Suspicious Koplik spots were noted in 1 case only. All of these children, as in the former group, showed absence of complications, toxicity, and catarrhal symptoms. Blood was withdrawn from 3 of the children receiving 6,000 or 600 $TCID_{50}$'s of vaccine for the determination of the presence of viremia. This was done on the third day after inoculation in 2 cases and on the

Table III. Determination of minimum antigenic dose of amniotic sac-grown vaccine

*Vaccination concentration**	*Child*	*Antibody titer†*	
		Pre	*Post*
6,000 $TCID_{50}$	1	< 4	16
	2	< 4	128
600 $TCID_{50}$	3	< 4	64
	4	8	256
60 $TCID_{50}$	5	< 4	44
	6	< 4	64
	7	< 4	27
6 $TCID_{50}$	8	< 4	44
	9	< 4	256
	10	< 4	22

*As determined by titration of the undiluted vaccine in Hela cell monolayers.

†This represents the reciprocal of the end point dilution.

Table IV. Responses in children with low prevaccination antibody levels

Child	*Antibody titers**		*Dosage of amniotic sac virus*
	Pre	*Post*	
1	8	8	6,000 $TCID_{50}$
2	16	16	6,000 $TCID_{50}$
3	8	8	6,000 $TCID_{50}$
4†	4	22	6,000 $TCID_{50}$
5‡	8	256	600 $TCID_{50}$

*This represents the reciprocal of the end point dilution.

†From Table I.

‡From Table III.

fourth day in the remaining child. It was not possible to recover the virus from the blood of any of these children.

Nine additional children who were considered immune because of the presence of antibodies were each given 1 ml. of undiluted amniotic sac vaccine in order to determine whether a rise in antibodies would occur in this group. None of these showed a rise in titer of neutralizing antibodies when their sera were tested 29 days after injection of the vaccine. Three of the children who did not respond serologically to vaccination had very low titers at the time of vaccination. In the entire study reported here there were 5 children whose titers ranged from 4 to 16 at the time of vaccination. Of these 5, only 2 responded with antibody production. The data are summarized in Table IV. No unfavorable effect on the tuberculous process was observed in any of the children immunized.

DISCUSSION

Our results in these early clinical trials indicate clearly that it is already possible by inoculation of attenuated live measles viruus to evoke a significant antibody response. The clinical manifestations vary from cases of considerably modified measles to those with no symptoms at all. Those who developed modified measles showed none of the more distressing symptoms of this disease. None of the children appeared toxic. There was an absence of cough, coryza, and conjunctivitis. No child showed evidence of the pyogenic complications associated with measles, such as middle-ear infection, tonsillopharyngitis, bronchitis, or pneumonia.

It is interesting to note that in most instances a booster response to vaccination was not observed in children who had antibody levels as low as 8 or 16 at the time of vaccination. Of the children vaccinated with the amniotic sac passaged virus, 20 had antibody titers ranging from less than 4 to 16. Of these children, 17 responded to vaccination with a rise in titer, and among them only 2 had demonstrable antibody at the time of vaccination; these were the only children who failed to show any clinical symptoms. In fact, none of the children (Table IV) who had demonstrable antibody at the time of vaccination manifested any clinical symptoms. While the number of children studied is small, these observations suggest that levels of antibody that are at the lower limit of detection by the virus neutralization test used, are sufficient to prevent clinical symptoms and in some instances to prevent infection.

We were unable to demonstrate viremia in the 3 cases investigated. This may be because the blood was obtained too early in the incubation period. It is also possible that when the virus is attenuated one cannot demonstrate viremia.[10]

Many questions still remain to be answered. Will these children remain permanently immune as in the naturally acquired disease? It may well be that some symptoms may indeed be necessary if the immunity produced is to be permanent. May encephalitis follow immunization with attenuated virus just as it does on occasion after the naturally acquired disease? One can only speculate on this point. The cause of measles encephalitis remains unknown. As might be expected, two theories predominate: a viral etiology and an allergic etiology. The only direct evidence in this respect is an observation by Enders[10] that measles virus could be isolated from the spinal fluid of monkeys inoculated with low-passage virus. No virus could be isolated when high-passage virus was inoculated. If future experience indicates the absence of the occurrence of encephalitis in chronologic association with the administration of live attenuated measles virus, then one of the most compelling reasons for a measles vaccine would be the prevention of measles encephalitis.

Another question that arises is whether children so immunized are contagious for a variable period of time. Measles is transmitted mainly by the droplet method as a result of coughing and sneezing. We have been unable to demonstrate the measles virus in nasopharyngeal swabs. It would seem that since there is an absence of catarrhal symptoms in those immunized with attenuated virus, these children are in all likelihood not contagious.

What is the best route of administration of attenuated measles virus? Our children were all immunized by the subcutaneous route. Other routes of administration should be explored. It would be of interest to study the effects of vaccine given intradermally or by the swabbing of the nose and throat.

SUMMARY

Early clinical trials indicate that it is possible to immunize children with live attenuated measles virus. The susceptible subjects develop either no symptoms at all or a modified measles with fever, leukopenia, and a faint eruption. Koplik spots are uncommon. These children have no catarrhal symptoms and do not appear toxic. All of the susceptible children developed a significant titer of neutralizing antibodies. No complications occurred in any of our cases. The urgent need of a measles vaccine is stressed, and there are indications that measles immunization as a routine procedure may not be too distant.

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A report of 16 tumors of the spinal cord in children; the importance of spinal rigidity as an early sign of disease

Frederick L. Richardson, M.D., M.R.C.P.*

BALTIMORE, MD.

THE OCCURRENCE of tumors involving the spinal cord in children is frequent enough to require the vigilance of all who are in pediatric practice. Commonly, early signs are missed and the diagnosis delayed until irreparable damage has been done. The apparent rarity of the disease is belied by the fact that more than a dozen articles related to it have been published during the last 10 years.

In most cases, the reward of diagnosis, even tardy, may be relief from intractable pain with complete remission of symptoms for many years or for life. Errors in diagnosis may result in progressive paraparesis and death.

Although Ross and Bailey[1] comment that "the prime requisite for recognition of a spinal cord tumor is suspicion of its existence," it is rare for suspicion to be aroused without previous association with a case of spinal cord tumor. In the numerous reports in the literature[1-10] the comment that tumors of the spinal cord may be about one-fifth as common as intracranial tumors under the age of 12 years[2, 11-16] would suggest that a pediatrician will rarely encounter such a tumor in his practicing life. If such a case does present, he may, in spite of careful examination and other investigations such as x-rays, fail to make the diagnosis and may even deny that the symptoms have any organic basis.

This paper does not represent a detailed review of symptoms and signs which already have been described. It stresses the importance of one valuable symptom and sign which the author believes to be present almost invariably, namely, *painful spinal rigidity*. This finding may persist for months or years in the absence of neurological signs.

The course of these tumors is too variable to permit an accurate estimate of prognosis either pre- or postoperatively, except on rare occasions. The major exception is when systemic disease, particularly of a malignant nature, has presented itself with involvement of the spinal cord or vertebrae. Thus the prognosis in any given child is individual and dependent upon the length of the history, the degree of neurological deficit, the nature of the lesion if determinable histologically, the extent of the tumor at the operation and the possibility of its removal, and the postoperative recovery and subsequent course.

*Address, Diagnostic and Evaluation Center for Handicapped Children, The Johns Hopkins Hospital, Baltimore 5, Md.

CASE MATERIAL

The records of patients 14 years of age and under admitted to the Hospital for Sick Children, Great Ormond Street, London, in the period from 1954 through 1958 and to the Harriet Lane Home from 1951 through 1959 have been reviewed. In addition to primary tumors within the spinal canal, invasive or metastatic tumors of the spinal column or its contents presented with similar manifestations are included. Cases associated with any visible or palpable external signs of congenital defect or anomaly such as lipomata, sinuses, moles, or hairy nevi involving skin over the spinal column or elsewhere are not included. (A review of the 16 cases is presented in Table I.)

CASE REPORTS

Case 1 (H. W., 5 years old). At 14 months this white girl would walk or stand only if lifted into the standing position but would then walk well. At 18 months she was reluctant to bend her back, and she picked up objects off the floor by keeping the spine erect and flexing the hips and knees. On rising from the floor she would occasionally "climb up" her legs.

At the age of 2½ years, although serial x-rays of the spine and tuberculin tests were negative, she was admitted to an orthopedic hospital and maintained on a frame and later in plaster with a provisional diagnosis of Pott's disease. Irritability was so marked that 6 months later she was discharged and a diagnosis of "functional nervous disorder" was made. At that time dorsal kyphosis and lumbar lordosis were present and a neurological examination was normal. At the age of 4 years she was again seen by an orthopedic surgeon and complained of backaches, but x-rays were still negative. Examination by a neurologist revealed an absence of tendon reflexes in the lower limbs.

One year later, when she was 5 years old and weighed 33 pounds, she was seen by a third orthopedic surgeon and on this occasion x-rays showed demineralization of the pedicles of the first and second lumbar vertebrae.

On admission to the hospital (H. S. C.) the cerebrospinal fluid was normal with a protein of 10 mg. per 100 ml. and normal manometry. A lumbar myelogram demonstrated a block with the lower level at L-3. Laminectomy (T-12 to L-2) revealed a grossly expanded dural sac. On opening the dura, a dermoid cyst was found adherent to the lower end of the spinal cord and roots. Necrotic sebaceous material was evacuated and the nonadherent part of the tumor removed.

The child made excellent postoperative recovery and 4 years later, apart from a lower thoracic lordosis, shows no abnormality on physical or neurological examination. There is no weakness of the lower limbs or abnormality of the tendon reflexes. Progress at school is satisfactory and the only symptom is the rare occurrence of urinary incontinence possibly associated with mild urinary infection.

Case 2 (J. M., 4 years, 9 months old). This white girl was admitted to hospital with a 7-month history of repeated attacks of neck and back stiffness. In the preceding summer, 2 weeks after her first poliomyelitis vaccination, she developed a mild upper respiratory infection. Three days later there was a sudden onset of neck rigidity with pain, headache, photophobia, pyrexia, and pain and weakness in the left thigh. On admission to a children's hospital, the cerebrospinal fluid contained 164 white cells per cu.mm., mostly lymphocytes; protein, 50 mg. per 100 ml.; and sugar, 40 mg. per 100 ml. The pyrexia lasted 2 days and this was followed by good recovery within 3 weeks, although the left leg tended to tire easily.

Two attempts to culture the poliomyelitis virus on Hela cells were unsuccessful and complement fixation tests showed no rise in titer with Types 1 and 3 virus. With Type 2 an initial titer of 1/128 fell to 1/64 after 3 weeks. One month later the child developed Sonne dysentery and made a rapid initial recovery. However, for sometime afterward, there were attacks of abdominal pain and constipation and she was pale and listless and complained of headaches.

Table I

Case	*Age, race, sex*	*Presenting symptom and original diagnosis*	*Diagnostic delay*	*Roentgenograms of spine*	*C.S.F. (mg./1*
1 (H. W.)	5 years, white F	Spinal rigidity and irritability; "climbing up legs"; Pott's disease	3½ years	Twice negative; then rarefied pedicles	0
2 (J. M.)	4 years 9 months, white F	Back and nuchal rigidity with CSF pleocytosis; poliomyelitis?	7 months	Repeatedly negative	0 ,000 ,000
3 (R. S.)	7 years, Negro F	Pain R buttock; osteoid osteoma? tuberculosis? psychogenic?	9 months	Slight scoliosis and lordosis on 2 examinations	208
4 (J. M.)	11 years 6 months, white M	Stiff painful back; "careful" gait; dislike of school?	2 months	Repeatedly negative	Blood fr
5 (M. J.)	7 years, white F	Sudden screaming attacks; spinal rigidity; Pott's disease?	1 year	Repeatedly negative	*Slightly
6 (B. G.)	10 years, white F	Head tilted to L; pain in back; weak left leg; CNS tumor?	1 year	Negative	186
7 (T. F.)	6 years 9 months, white F	Painful stiff neck; cervical subluxation? bulbar signs; brain stem tumor?	2½ months	Thoracolumbar scoliosis; absent pedicles T-8 to 1	1,720
8 (J. M.)	2 years 3 months, Negro M	Weak legs; pain in left leg; "climbed up legs"; muscular dystrophy	5½ months	Negative	18
9 (D. G.)	1 year 3 months, white M	Vomiting, fever, weak arms, head tilt, stiff neck; poliomyelitis?	3 months	Reported negative	2,560
10 (R. B.)	14 years, white M	Attacks pain thoracolumbar region; paraplegia	1½ years	Negative	83
11 (B. J. L.)	11 years 9 months, white F	Stiff neck with pains in shoulders; weak arm and leg; paraplegia	1 year	Pedicles C-8 to T-1 rarefied and interpediculate space widened	1,660
12 (R. H.)	1 year 9 months, white M	Adrenogenital syndrome; irritable with stiff neck; paraparesis	9 months	Repeatedly negative	700
13 (R. R.)	6 years 3 months, Negro M	Irritable for months and then rigid back; Pott's disease?	6 months	Collapse T-8; abscess?	400
14 (A. B.)	2 years 5 months, white F	Pain in left leg and limp; rigid spine; tuberculous hip?	3 months	Possible effusion left hip; later destruction S-1	130
15 (G. M.)	13 years 4 months, white F	Cramps in right leg with limp and wasting; poliomyelitis?	7 months	Negative spine and pelvis	Pandy n
16 (P. B.)	3 years 6 months, white F	Extreme irritability; rigid back with pain on walking; Pott's disease?	5 months	Wedging L-4 to 5 with later local changes	Not don

C.S.F. protein (mg./100 ml.)	Level of block on myelogram	Operative findings and pathology	Outcome and duration of follow-up
0	L-3	Dermoid cyst	Full recovery; 3 years
0 1,000 5,000	L-3	Cystic ependymoma	Full recovery; 2 years
208	Above L-3, below L-4	Meningioma?	Full recovery; 7 years
Blood from trauma	Above T-12, below L-1	Subependymal glioma	X-ray therapy; full recovery 2 years
"Slightly elevated"	L-3	Ependymoma?	X-ray therapy; full recovery 3 years
186	T-3 to 4	Neurofibroma	Full recovery; 2 years
1,720	T-8	Syrinx of cord (aspiration); no biopsy	X-ray therapy; full recovery; 2½ years
18	1 doubtful, 2 block T-6	Meningioma? angioma?	Attends school; wears braces; 8 years
2,560	T-7	Intramedullary tumor; unidentified	X-ray therapy; doing well; 4 years; mild kyphoscoliosis
83	T-10	Hemangioma?	Full recovery; attends military academy
1,660	T-2	Neurofibroma	Won figure skating competition in Canada; 7 years
700	T-4	Lipoma	Crawling; walking with support; 2 months
400	Not done	Anaplastic, probable osteogenic sarcoma	X-ray therapy; died after 3 months
130	L-4	Initial, fibrosarcoma; final, neuroblastoma	X-ray therapy; died after 14 months
Pandy negative	Not done	Biopsy; retroperitoneal sarcoma? neuroblastoma?	Nitrogen mustard, x-ray therapy; steady improvement 2 years
Not done	Not done	After 5 months slight anemia; marrow became leukemic	Antifolic and steroid medication; no deterioration after 1 year

Two months later the patient developed a respiratory infection followed after 4 days by severe headache again, accompanied by marked stiffness of the neck and back, pyrexia, and photophobia. Routine roentgenograms of the patient's skull, spine, and chest were negative. The cerebrospinal fluid was xanthochromic and contained 32 white cells per cu.mm., and the protein concentration was 1000 mg. per 100 ml. Two days later the cerebrospinal fluid was clear and contained 18 white cells per cu.mm. and the protein concentration was 180 mg. per 100 ml.

The patient was transferred to another hospital where her third attack of neck and back stiffness associated with fever developed. Neurological examination again demonstrated weakness of the left quadriceps with an increaed left knee jerk and lumbar puncture again produced xanthochromic fluid with a protein of 500 mg. per 100 ml. The patient was sent home for further observation. While at home she was fairly well except for weakness of the left leg and pain in the left thigh which disappeared with exercise. At this time the child's whole back was stiff and it was extremely difficult for her to touch her toes with her hands.

In the sixth month of the illness, the patient developed a fourth attack of neck and back stiffness with fever and photophobia which was resolved without treatment. However, she was admitted to hospital (Neurosurgical Unit H. S. C.) where examination revealed a rigid back which was painful on flexion, weakness of the left lower limb with increased deep tendon reflexes, and bilateral extensor plantar responses. An electroencephalogram suggested distortion of deep midline structures, but a ventriculogram was normal. A lumbar puncture was attempted in the intervertebral spaces of L-2 to 4 but without success until 3 ml. of viscid, blood-stained cerebrospinal fluid were obtained from the intervertebral space between L-5 to S-1. Manometry was impossible and 2 ml. of contrast medium as injected showing a complete obstruction at the lower level of L-3.

A laminectomy (L-1 to 4) revealed a large soft vascular cystic ependymona. The child was discharged in good condition 8 days later and walked without undue weakness of the legs. This progress has continued.

Case 3 (R. S., 7 years old). This Negro girl complained of pain in the right buttock in the right gluteal region at night. Her gait was normal and a neurological examination was normal. An x-ray of her pelvis and lumbar spine showed a mild lumbar scoliosis. During the next 2 days she complained on 3 occasions of inability to sleep due to pain in the right hip and difficulty in sitting on the right buttock. A difficult examination revealed that the child's back was stiff and she could not be reassured although she walked well. The following day she developed a limp and x-rays of spine were repeated and reported as being normal. The following day the patient complained of pain in the right leg on coughing and walked with a persistent lordosis. Three days later the patient returned for a myelogram but as she had apparently recovered she was discharged and the diagnosis was deferred.

Nine months later the child again appeared complaining of pain in the lower back and right hip of 2 weeks' duration with some numbness of the thighs. A few days later she was still complaining of the same pain and was thought to be hysterical. A repeat neurological examination revealed no abnormality, but 2 days later, in view of her continued complaint of pain and discomfort, she was admitted to hospital.

On admission she was pleasant but was "afraid to move about." Neurological examination revealed an absence of deep tendon reflexes in the lower limbs and flexor plantar responses, but pain occurred in the right thigh on correcting the lordosis or extension of the right leg. A lumbar puncture revealed a protein of 208 mg. per 100 ml., with normal manometric responses except for opening pressure of 270 mm. A cisternal myelogram demonstrated a complete block at the upper level of L-3 and a lumbar myelogram showed complete block at L-4. A laminectomy (L-1 to 4) revealed a cherry-sized intraspinal irregular mass which was firmly adherent to a small nerve root of the cauda equina.

Although in many microscopic sections the tumor appeared to be a neurinoma, calcification was present, suggesting that the tumor was possibly meningeal in origin. The child has progressed well since operation.

Case 4 (J. M., 11 years 6 months old). This white boy complained of pain in the lumbar region for 8 weeks accompanied by a stiff, painful back. Examination of the patient revealed no neurological signs. Roentgenograms of the vertebral column were normal and a lumbar puncture revealed blood-stained spinal fluid from a traumatic tap. However, myelograms showed a block with the upper level of T-12 and the lower level of L-1. A laminectomy revealed a large subependymal glioma of the filum terminale which was excised. Years later a neurological examination was normal and no skeletal deformity was noted. The patient was making good progress at school and playing games occasionally.

Case 5 (M. J., 7 years old). At 2½ years this white girl developed a pulmonary tuberculous primary complex. Streptomycin injections were associated with the formation of an abscess in the right buttock and scar formation. The patient made complete recovery from this illness but 1½ years later sudden screaming attacks began and she complained of pain in her back and was no longer able to run. The attacks of pain were of sudden onset by night or day during which time she refused to sit or stand. After 9 months she was admitted to the hospital with a provisional diagnosis of Pott's disease. On examination, spinal rigidity was noted but her roentgenograms of the spine were normal. Treatment was given on a plaster frame for 3 months with some improvement, but the spinal rigidity remained. Two lumbar punctures were done and each reportedly showed a "slightly elevated" protein. A lumbar puncture and myelogram demonstrated a space-occupying lesion at the level of L-3 and a cerebrospinal fluid protein content of 70 mg. per 100 ml. A laminectomy revealed a tumor intimately involving the cauda equina. A biopsy was not done and the tumor was thought, on macroscopic examination, to be an ependymoma. The decompression was followed by x-ray therapy with improvement which has been maintained for 3 years. Recently, minimal evidence of sphincter disturbance has appeared which may be organic in origin.

Case 6 (B. G., 10 years old). This white girl developed a torticollis 6 months prior to admission and held her head turned and tilted to the left side. The patient complained of pain in the back toward the end of the day, before going to sleep at night, and on awakening. Five months later she became unsteady on her feet and occasionally fell to the left, complaining that her left leg gave way. Subsequently she noticed "pins and needles" in both legs and complained of the left leg "feeling sleepy." On physical examination she was irritable and uncooperative, her left leg was weaker than the right, and she had increased deep-tendon reflexes with an extensor plantar response in this limb. An exaggerated lumbar lordosis with scoliosis was present, and roentgenograms of the spine and skull were negative apart from some postural deformity. A lumbar puncture was done which revealed a protein of 186 mg. per 100 ml., and a myelogram showed a block at the T-3 to 4 level. A right hemilaminectomy revealed a poorly pulsating spinal cord, and no extradural obstruction could be demonstrated inferiorly. The myelogram was repeated and 10 days later the laminectomy was extended and a neurofibroma was easily removed from within the arachnoid space at the T-6 level.

The patient made good postoperative recovery and is now functionally normal.

Case 7 (T. F., 6 years 9 months old). This white girl fell and subsequently complained of pain and stiffness of the neck which lasted for 2 months during which time a cervical subluxation was considered but not confirmed. One month later vomiting and loss of weight occurred and roentgenograms of the patient's spine and chest were negative apart from a thoracolumbar scoliosis. One week later the patient showed progressive listlessness and had difficulty in swallowing her saliva. The child then developed a

staggering gait and a brain stem tumor was suspected. A tracheotomy was performed because of the bulbar symptoms. A lumbar puncture revealed a protein of 1720 mg. per 100 ml. and a lumbar myelogram demonstrated a block at T-8 with an increase in the interpediculate distance at the T-8 to 10 level. A review of the earlier films showed absence of the pedicles at the T-6 level. A laminectomy was done (C-1 to 3) which revealed a distended spinal cord and needle aspiration of the cord and a dorsal split made in the cord released approximately 15 ml. of xanthochromic fluid.

The patient made good postoperative recovery and x-ray therapy was given. Subsequent examinations of the patient have revealed no abnormality for 2½ years.

Case 8 (J. M., 2 years 3 months old). This patient was a Negro boy who walked at 10 months but at 22 months "he walked as if his legs wouldn't hold him" and he would stumble and fall. Three months later he complained of pain in his left leg. On examination he was well nourished but had a symmetrical waddling gait, lumbar lordosis, and a protuberant abdomen. It was noticed that upon rising from the floor he "climbed up his legs." His thigh and leg muscles were "well developed" with good power and the deep-tendon reflexes were increased in the lower limbs with bilateral extensor plantar responses. Roentgenograms of the patient's hips and spine were reported as normal and the provisional diagnoses at that time were pseudohypertrophic muscular dystrophy, progressive spastic diplegia, or possible Friedreich's ataxia. A lumbar puncture showed normal cerebrospinal fluid dynamics with a protein of 18 mg./100 ml., and a muscle biopsy was normal. The patient was seen by an orthopedic surgeon who suggested repeating the x-rays of the spine and a lumbar myelogram.

Two months later a myelogram showed fragmentation of the dye in the cervical and thoracic region, though it was not thought to be significant. A skin resistance test was done which suggested a T-6 level and the patient had a further myelogram which confirmed a block at the T-6 level. At operation, cervical laminectomy revealed an "inflamed" arachnoid area which was stripped and which clinically suggested a meningioma or angioma. The patient was walking well and was discharged 2 weeks later. Three months later the symptoms recurred but on examination no change in neurological signs could be detected and a myelogram was entirely normal, as was the cerebrospinal fluid. The patient has made steady progress since that time and now attends school regularly wearing leg braces.

Case 9 (D. G., 1 year 3 months old). This white boy walked with support at 7 months and unsupported at eleven months. At the age of 8 months he had a "virus attack" with vomiting and fever for 3 to 4 days and on examination he was thought to be "weak in his arms." Three months later his left arm, which "hung by his side," was used infrequently and he held his head tilted to the right. The grip in his right hand was also thought to be weak. On examination three months later he was well nourished but resented movement of his head. The upper limbs were wasted and weak with absent deep tendon reflexes, the leg deep tendon reflexes were increased, persistent ankle clonus was present bilaterally, and the sensation was normal. Roentgenograms of his spine were negative and lumbar puncture combined with a myelogram revealed xanthochromic cerebrospinal fluid (protein content 2,560 mg. per 100 ml.) with normal dynamics and a complete block at T-7. A laminectomy (C-5 to T-7) was performed which revealed an enlarged spinal cord at the C-4 to 5 level; beneath the dura the spinal cord appeared infiltrated with bluish-gray tissue. An aspiration was negative, and a biopsy was made at the D-3 level. The dura was left open and the wound closed. The lesion was not identified histologically. X-ray therapy was given for over 3 weeks (2,500 r at 4 cm. depth) and the child's irritability steadily decreased. At the last follow-up the patient was essentially normal apart from a mild kyphoscoliosis for which a spinal jacket has been fitted.

Case 10 (R. B., 14 years old). This white boy from a physical training academy had paraplegia of 1 week's duration. One and one-half years prior to the paraplegia he complained of sudden pain in the lower thoracic region which lasted for 1½ hours and then disappeared. Some months later he complained of pain in the lumbar region and stiffness of the back on rising. Twelve days prior to admission he developed sudden pain with loss of the power and sensation in the legs, followed by a paraplegia.

On examination he was well nourished but had a rigid back and neck with tenderness on percussion over the lower dorsal vertebrae. A possible sensory level to pinprick was elicited at T-11. The roentgenograms of his vertebral column were normal. A lumbar puncture revealed slowing of the normal manometric responses and a cerebrospinal fluid protein content of 83 mg. per 100 ml. A lumbar myelogram revealed a complete block at the T-10 level. A laminectomy (T-7 to T-11) showed a dark red extradural mass which peeled out easily and the microscopic examination suggested a hemangioma with vascular tissue containing inflammatory cells, fibroblasts, eosinophils, hemosiderin-laden macrophages, and proliferating capillaries. X-ray therapy was given over 4 to 5 weeks (4,000 to 5,000 r) and excellent postoperative progress resulted. At last follow-up the patient was attending a military academy.

Case 11 (B. J. L., 11 years 9 months old). A white girl 1 year prior to admission complained of sudden stiffness in the lower cervical region radiating to both shoulders with weakness of the right arm for a few days. This discomfort persisted variably for 11 months when she stumbled and fell. On examination, the right leg was found to be weak and soon afterward the left leg showed weakness as a paraparesis developed with some sphincter difficulties. The patient was admitted to hospital where on examination a paraplegia in flexion was present with lower intercostal retraction and nuchal rigidity. Percussion of the C-8 to T-1 region was painful to the patient. Roentgenograms of the spine showed increased interpediculate spaces with demineralized pedicles and a myelogram combined with lumbar puncture revealed a complete block at the T-2 level and a cerebrospinal fluid protein of 1,660 mg. per 100 ml. A laminectomy was performed (C-5 to T-2) and a grayish intradural extramedullary tumor 3 by 1½ cm. in size and resembling a neurofibroma was removed. The patient was discharged 1 month later and she was able to walk a few steps with assistance. Seven years later she won a figure skating competition in Canada.

Case 12 (R. H., 1 year 9 months). This patient had a known salt-losing adrenogenital syndrome and for 9 months had been observed to hold the neck stiffly. Two months prior to this routine admission for evaluation of his adrenogenital syndrome his walking slowed and he cried with pain if encouraged to walk. On examination he was extremely irritable and screamed on being picked up. He refused to pick up toys from the floor; this had been noted by his parents for some months. Weakness of the lower limbs with pyramidal signs was present, and an easily palpable anhidrosis (confirmed with an iodine test for starch) suggested a lesion at the C-3 to 4 level. A myelogram demonstrated the lower level of the block to be at T-4 (cerebrospinal fluid protein 700 mg. per 100 ml.) and a dorsal laminectomy revealed a long thin lipoma adherent to the cord beneath the arachnoid. The lipoma had no capsule and it was difficult to remove. The patient's paraparesis increased slightly postoperatively, but he improved and was discharged 3 weeks after operation and was able to walk a few steps with considerable support. It is reported that he is continuing to improve.

Case 13 (R. R., 6 years 3 months old). For 6 months this patient was noted to be miserable and irritable, but the family doctor could find no abnormality. Two weeks prior to admission he was observed to pick up objects from the floor while holding his back rigidly, flexing the knees and hips but not the spine. The child complained of severe backache, and a neurological examina-

tion revealed signs of involvement of the pyramidal tract with extensor plantar responses which progressed within a few days to a paraparesis. In addition to the paraparesis the patient exhibited flattening of the dorsal spine with spinal rigidity and tenderness to palpation in the middorsal region. A roentgenogram revealed collapse of the eighth thoracic vertebra with possible formation of an abscess. A myelogram was not done, but laminectomy was performed and revealed a purple-colored tumor on the posterior aspect of the spinal cord which was vascular and friable and which proved to be a highly malignant anaplastic growth, possibly an osteogenic sarcoma. X-ray therapy was given but the patient died 3 months after operation.

Case 14 (A. B., 2 years 5 months old). This white girl had pain in the left leg accompanied by a limp for 3 months. She had been seen to retrieve objects from the floor by flexing the knees and hips and keeping her spine rigid. The parents reported that she was extremely irritable and losing weight. Roentgenograms of the patient's pelvis showed possible fluid in the left hip and later x-rays showed irregular destruction of the first sacral vertebra. Examination of the patient revealed extreme irritability with spinal rigidity, but no neurological signs were present. Lumbar puncture showed normal manometric responses with a cerebrospinal fluid protein content of 130 mg. per 100 ml. A myelogram demonstrated obstruction at the level of L-4 and a lumbosacral laminectomy revealed an extradural tumor, possibly a fibrosarcoma. However, orbital tumors developed and review of the pathologic material suggested neuroblastoma. Further metastases occurred and the patient died 1 year after operation.

Case 15 (G. M., 13 years 4 months old). This white female developed cramps in her right calf and complained of fatigue. After 5 months the patient was admitted to hospital with a painful right hip and loss of weight. On examination she was found to have a wasted right leg with diminished tendon reflexes and a diagnosis of poliomyelitis was made. A lumbar puncture revealed normal cerebrospinal fluid dynamics, no cells were present, and the Pandy test was negative. Six weeks later the patient was found to have sensory disturbance in the limb associated with thoracolumbar spinal rigidity and tenderness and a rectal examination revealed a palpable irregular mass. The patient was transferred to hospital (JHH) where a biopsy on examination suggested a probable neuroblastoma. Nitrogen mustards and x-ray therapy were given and the patient has made steady improvement with gain in weight during the last 2 years.

Case 16 (P. B., 3 years 6 months old). For 3 months this white girl complained of lower back pain increased by walking and her parents noticed her loss of energy and appetite. On examination, all that could be found was extreme irritability and the fact that she retrieved objects from the floor keeping the back rigid and the knees flexed. The neurological examination was normal. Roentgenograms of the patient's spine suggested minimal wedging of the L-4 to 5 vertebrae. The patient's blood count was normal apart from a hemoglobin of 7 Gm. per 100 ml. and the bone marrow was also normal. During the next 2 months the patient showed spontaneous improvement with a good gain in weight and an increase in her hemoglobin concentration to 9 Gm. per 100 ml. One month later, however, she deteriorated and repeat roentgenograms confirmed the wedging of the fourth and fifth lumbar vertebrae with new changes in other vertebrae. The blood count revealed a hemoglobin of 8 Gm. per 100 ml., leukocytes 2,800 per cu.mm., with a normal differential, and the platelets 140,400 per cu.mm. A further bone marrow aspiration showed "95% blasts" and the patient was treated for leukemia with no deterioration 1 year later.

DISCUSSION OF CASE MATERIAL

The majority of the patients in this series had nonspecific symptoms, such as irritability or loss of weight, which were at first not correlated with the site of the lesion. Neurological signs were usually absent or so min-

mal that the possibility of disease of the spinal cord or vertebral column was incorrectly excluded unless obvious and gross signs of involvement of the spinal cord developed at a later date.

The author believes that certain signs are so suggestive of involvement of the meningeal or nervous tissue that their persistence should lead to a firm diagnosis of organic disease of the spinal column or its contents.

One symptom and demonstrable sign stands pre-eminent in the majority of cases, namely *the presence of painful spinal rigidity,* often of a chronic nature and usually associated with irritability. It is submitted that this is always a sign of organic disease of the vertebral column or its contents. The sign was present in all of the cases herein described and it is suggested that it should be looked for in chronically irritable children who are "unwell" without evidence of involvement of a specific system. If any evidence is present of scoliosis or deformity, reversal of spinal curvature, or neurological signs the indication is of particular importance. A full range of rotary spinal movements may often be achieved slowly, but flexion, which diminishes the spinal canal volume causing increase in intradural tension, is resented. Extension of the spine may also be painful.

Of the symptoms encountered, irritability, apprehension and resentment of movement on being picked up, listlessness, anorexia and weight loss, sudden screaming attacks which subsided rapidly, muscular weakness sometimes associated with elevation of the temperature, urinary incontinence, and a "waddling gait" and "walking up the legs" were common. Several children when picking up objects from the floor were noted to keep the vertebral column rigidly extended and to flex the knees, never flexing the spine. Others, for weeks or months, persistently refused to pick up favorite playthings from the floor.

Of 3 children not otherwise recorded here, referred for "hysterical symptoms" and backache, 2 had tuberculosis with formation of a cold abscess, the other Scheuermann's disease.

In infants, Buchanan[17] observed that patients with tumors of the spinal cord are the most easily confused with infants with either the amyotonia congenita syndrome or anterior poliomyelitis. In all 6 infants recorded by him, however, the initial complaints reported were stiffness of the neck or back, with pain on movement of the trunk, not seen in the amyotonia congenita syndrome.[18-20] In those children with intramedullary tumors, anhidrosis was found below the level of the tumor and it is possible that where a gross neuroiogical deficit is not present this may be suggestive evidence of an intramedullary lesion. One patient mentioned here (Case 12) demonstrated a palpable anhidrosis. However, the tumor was an extramedullary intradural lipoma compressing the cord from C-4 to T-4 with minimal pyramidal tract signs.

ROENTGENOGRAPHIC FINDINGS

Radiologic examination of the vertebral column in children with unexplained back pain should include specific examination for demineralization or absence of the vertebral pedicles, widening of the interpediculate distance,[21] and reversal of the normal spinal curvature or variation of the curvature. Retrospective examination of the original x-rays has frequently revealed that they were not "negative" or "normal" as reported.[2, 5, 8, 10, 22]

LUMBAR PUNCTURE AND MYELOGRAPHY

The varied diagnostic criteria which have been described in previous papers to establish the clinical diagnosis of tumor of the spinal cord by means of sensory or sweating levels, dissociated anesthesia, or analgesia[4] are of only relative importance. Once search is begun, the existence of the tumor is already suspected and the technique by which the diagnosis is made should be an attempt to demonstrate deformity of the spinal cord. If on lumbar puncture there is a poor flow of cerebrospinal fluid on jugular compression and the cerebrospinal fluid protein content is elevated, a myelogram is indicated to determine the site of the tumor. A possible

exception is perhaps where there is evidence of metastatic disease from a primary site elsewhere.

Where signs of paraparesis exist there is a danger that puncture of the spinal theca may precipitate a paraplegia and neurosurgical advice should be sought before commencing the procedure.

It is of interest to note that 2 of the patients in this series had normal cerebrospinal fluid protein concentrations and normal manometric responses on jugular vein compression, as have other reported cases.[5, 23] There is some experimental evidence that the manometric dynamics of cerebrospinal fluid in the presence of a partial block is dependent upon the cross section of the patent subarachnoid space around the tumor. If the cross section of the bore of the needle inserted into the spinal theca is equal to, or smaller than, the space about the tumor, no evidence of a block may be obtained manometrically.[24] It is important to note, however, that in no case described here, or noted elsewhere, did myelography fail to demonstrate accurately the lower or upper level of the tumor, whether a radiopaque medium or air was used for the myelogram.

It is not justifiable to delay myelography for weeks or months, during which time the patient may be in considerable pain, until serious deterioration gives additional clinical or neurological signs. If a myelogram is technically or otherwise unsatisfactory it should be repeated.

The dangers of myelography have been frequently overemphasized. Since the time of Dandy[25] this procedure has been used successfully in adults and children. As with any serious diagnostic procedure it should be performed by an experienced neurosurgical or radiologic team.

ERRONEOUS DIAGNOSES

Among the many erroneous diagnoses quoted, one of the most common and dangerous to the patient is that of anterior poliomyelitis.[1, 5-8, 22, 23, 26] The occurrence of fever and pleocytosis is not uncommon and, as in 1 patient (Case 2), it must be emphasized that the remission of signs with bed rest is not against the diagnosis of a tumor of the spinal cord. There are many reports in which the diagnosis of anterior poliomyelitis was persistently adhered to in patients where considerable variations in the signs occurred from week to week, where the deep-tendon reflexes were hyperactive and not diminished or lost, and where the spinal fluid protein was unusually high and increasing. Formidable and disturbing lists of misdiagnoses of children with tumors of the spinal cord have been recorded elsewhere.[5, 8]

Atlantoaxial dislocation following upper respiratory infections with demineralization due to soft tissue hyperemia can only be diagnosed with certainty if clear roentgenographic evidence of true dislocation is obtained. Where such evidence is not available a myelogram may be revealing. Although the major sign of 1 (Case 7) was torticollis the obstruction was in the midthoracic region (Fig. 1) and 4 (Cases 6, 7, 9, and 12) had "tilting" of the head associated with nuchal rigidity.

EXTRAMEDULLARY INVASION OF THE SPINAL CANAL

In the absence of trauma, dramatic signs accompanied by severe progresisve back pain of short duration with paralysis in the lower or upper limbs and with no evidence of inflammatory disease, such as epidural abscess, are unpleasantly suggestive of extramedullary compression of the cord. Such signs may well represent erosion or invasion by systemic disease such as neuroblastoma, leukemia, or, alternatively, a highly malignant local lesion of the cord or spinal column.[2, 4, 27] This point is illustrated in 4 patients (Cases 13 to 16) in this series.

The converse is fortunately true in that a long history with poorly defined or minimal signs, such as persistent back stiffness and scoliosis, may denote an intraspinal tumor with a good prognosis.

PROGNOSIS

The remarkable number of tumors of the spinal cord which have behaved in a benign

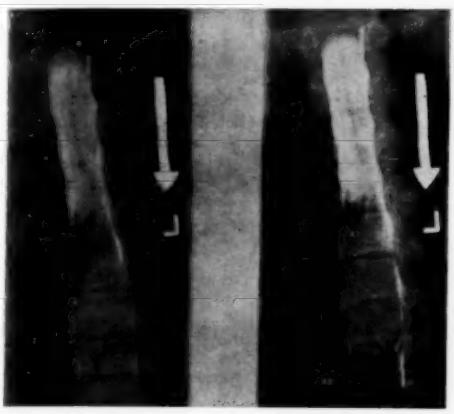

Fig. 1. A lumbar myelogram demonstrating almost complete obstruction of opaque dye at T-8 level (Case 7). There is demineralization or absence of the vertebral pedicles (T-8 to 10) alongside the tumor area with marked increase in interpediculate distances.[21] These changes are commonly found on retrospective examination of the initial roentgenograms.

fashion is surprising, even among those tumors not always so considered. Almost all patients, including some with extramedullary invasion of the spinal canal, have been given long periods of relief by simple decompression and "cure" has occurred for many years as a result of decompression alone if the site of the tumor was too serious to warrant any attempt at removal. In general, better results occurred in the cases where a partial or complete removal of the tumor was possible, as with some ependymomas of the cauda equina region where the cord itself was not always intimately involved.[1-10, 16, 17, 22]

The fate of the patients and the natural history of the disease based on groups of individual tumors are finely documented by Woltman and others[28] with a maximum postoperative follow-up of 38 years. This is complemented more recently by Wood and associates[29] who suggest that decompression, with careful limited removal of tumor tissue, if feasible, should be followed by x-ray therapy regardless of the pathologic condition of the glioma present, since the tolerance of normal spinal cord tissue has been better defined. The presence of a syrinx does not preclude x-ray therapy because of the high incidence of associated spinal cord neoplasms with syringomyelia.[30]

RESIDUAL DEFORMITY

Scoliosis associated with spasm of the erector spinae muscles or cervical muscles usually decreased and may return to normal after operation. This is naturally dependent upon the length of time the deformity was present during the growth period and the extent of the residual bony destruction or muscle paresis.[8, 11]

RECURRENCE OF SYMPTOMS

A number of children have had recurrence of symptoms since operation, such as bed-wetting or sudden screaming in the night which have been labeled as hysteria secondary to operation or previous organic illness and hospitalization. It is important to remember that these symptoms were present in many children during the course of their original illness and that such symptoms may recur if the tumor progresses or has not been removed completely.

SUMMARY

The case histories of 16 children with tumors involving the spinal cord are reported. The diagnoses were difficult. It is the belief of the author that a tumor involving the spinal cord, giving rise to symptoms, will almost invariably be accompanied by persistent spinal rigidity and irritability.

Although intramedullary and intradural tumors were not diagnosed for months or years in spite of repeated examinations and investigations, the outcome was excellent once the diagnosis was made.

Extradural involvement of the spinal cord tended to produce more rapid compression of the cord with paraplegia and by nature of the systemic disease involved often had a poorer prognosis.

Routine investigations, such as x-rays of the vertebral column, are regarded too frequently as satisfactory evidence of the absence of disease. A more specific examination of these x-rays is suggested, as in many cases,

a retrospective examination of the original films, usually reported as normal, showed conclusive evidence of disease.

On occasion, in the presence of a tumor of the spinal cord, the data from lumbar puncture may be normal. A myelogram should be done where a spinal cord tumor is suspected as in experienced hands it is a safe and essential procedure.

The possibility of hysteria frequently arises. It is of importance to demonstrate that the child is hysterical and to remember that hysteria may coexist in a situation of painful organic disease.

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Comparison of ocular reactions with the use of silver nitrate and erythromycin ointment in ophthalmia neonatorum prophylaxis

Joseph R. Christian, M.D.*

CHICAGO, ILL.

ACCORDING to the Rules and Regulations for the Control of Communicable Diseases of the State of Illinois[1] "it shall be the duty of any physician, midwife or nurse who attends or assists at the birth of a child, to instill or have instilled in each eye of the newborn baby, as soon as possible and not later than one hour after birth, a one per cent (1%) solution of silver nitrate or some other equally effective prophylactic for the prevention of ophthalmia neonatorum approved by the State Department of Public Health. The Illinois Department of Public Health approves only 1% silver nitrate solution as a prophylactic for ophthalmia neonatorum."

Many State Departments of Public Health have similar rules and regulations. From time to time, however, the effectiveness of silver nitrate, as well as the morbidity it produces, has been questioned by most individuals using silver nitrate as a prophylactic agent. It is the purpose of this paper to present the results of a study with silver nitrate and erythromycin ophthalmic ointment.*

MATERIAL AND METHODS

This study was carried out in the Newborn Nurseries of Lewis Memorial Maternity Hospital, Chicago. An attempt was made to alternate infants irrespective of type of delivery, prematurity, race, etc. A total of 4,292 infants were observed during a period of 1 year beginning June, 1958, and ending June, 1959.

The group receiving silver nitrate prophylaxis totaled 2,359 and the group receiving erythromycin totaled 1,933. The discrepancy in the two groups resulted from difficulty in initiating the routine of alternating patients during the first 2 months of the study. After the first 2 months, however, all patients were alternated.

The procedure for instillation of the medication was as follows:

Silver nitrate group. As soon after birth

*Address, Department of Pediatrics, Stritch School of Medicine, Loyola University, 706 South Wolcott Street, Chicago 12, Ill.

*Ilotycin ophthalmic ointment, Eli Lilly and Company (erythromycin 5 mg. per gram).

Table I. Incidence of ocular discharge according to month

	Silver nitrate			*Erythromycin*		
	Total	*Reactions*	*Per cent*	*Total*	*Reactions*	*Per cent*
June	193	(31)	16	136	(10)	7
July	177	(9)	5	162	(3)	2
August	219	(24)	11	168	(11)	7
September	198	(20)	10	152	(11)	7
October	201	(30)	15	157	(15)	10
November	170	(17)	10	140	(5)	4
December	183	(15)	8	147	(2)	1
January	196	(20)	10	162	(3)	2
February	165	(8)	5	151	(6)	4
March	169	(9)	5	141	(4)	3
April	186	(12)	6	157	(1)	6
May	174	(27)	15	155	(4)	3
June (1 to 21)	128	(15)	12	105	(3)	3
Total	2,359	(237)	10	1,933	(78)	4

Table II. Incidence and percentage distribution of ocular discharge according to sex

	Silver nitrate			*Erythromycin*		
	Total	*Reaction*	*Per cent*	*Total*	*Reaction*	*Per cent*
Male	1,169	124	16	945	29	3
Female	1,190	113	9	988	49	5

Table III. Incidence of reactions according to race

	Silver nitrate			*Erythromycin*		
	Total	*Reaction*	*Per cent*	*Total*	*Reaction*	*Per cent*
White	945	97	10	957	39	4
Negro	1,414	140	10	976	39	4

as feasible, but not later than 10 minutes and before any attempt at bathing, the brows, eyes, and nose of the newborn infant were wiped carefully but thoroughly with absorbent cotton. Then 1 to 2 drops of 1 per cent silver nitrate, supplied by the Illinois Department of Public Health in wax ampules, was instilled into each eye, which had been opened gently so that the solution reached all parts.

Erythromycin group. The technique was identical with that used in the silver nitrate group. A special wax ampule, similar to the one used for silver nitrate, contained the erythromycin ointment. Approximately a 1 cm. strip was used in each eye.

The period of observation of all infants, except premature or full-term infants with some disturbance requiring prolonged hospitalization, was 4 to 5 days postpartum. The eyes of each infant were examined daily by a pediatric resident and reactions were reported as follows: 0, no reaction; I, redness and swelling; II, redness and swelling plus

discharge; and III, redness and swelling plus copious purulent discharge. These standards for grading conjunctival reactions are identical with those utilized by Wachter and Pennoyer.[2] Cultures were taken on those having reactions II or III. The material for culture was taken with a dry sterile cotton swab from the inside of the lower lid margin and placed into Brewer's culture medium for 24 to 48 hours. At the end of this time, after Gram staining and after a screening examination, the material was subcultured on blood agar or another suitable medium.

RESULTS

Incidence according to month. Table I indicates the total number of patients observed and the incidence of eye reactions according to the month of occurrence. The over-all incidence rate of 10 per cent varied from 5 to 16 per cent in the silver nitrate group. In the erythromycin group, however, the over-all incidence rate was only 4 per cent, with a range of 0.6 to 10 per cent.

The peak incidence occurred in June, October, and May in the silver nitrate group and in October in the erythromycin group.

Incidence according to sex. Table II indicates the incidence and percentage distribution of ocular discharge according to sex. In the silver nitrate group, 124 reactions occurred in 1,169 males (16 per cent) as compared to 29 reactions in 945 males (3 per cent) in the erythromycin group. Among the female infants, 113 reactions occurred in 1,190 (9 per cent) of the silver nitrate group and 49 reactions in 988 (5 per cent) of the erythromycin group.

Incidence according to race. In Table III a comparison of the incidence of reactions according to race is presented. The percentage distribution of ocular reactions in the white and Negro infants was identical in the silver nitrate group (10 per cent) and in the erythromycin group (4 per cent), i.e., there was no difference on the basis of race.

Incidence according to severity. Table IV indicates the total number of patients with reactions according to clinical severity as well as to the number of positive cultures in the three grades of severity.

Silver nitrate group. Ten per cent (237) of the 2,359 patients receiving silver nitrate developed reactions. Thirty-one of these were found to have positive cultures; 206, however, failed to produce any growth on culture.

Redness and swelling (I) were reported in 129 infants, but positive cultures were obtained from only 6 of them.

Redness, swelling, and discharge, which was usually serous (II), were noted in 97 infants and 22 of these revealed bacterial growth when cultures were taken.

Redness, swelling, and a copious purulent discharge were found in 11 infants but only 3 of these produced positive cultures.

Erythromycin group. Four per cent (78) of the 1,933 infants in this group had ocular reactions. Cultures from these patients were positive in 13; no growth was demonstrable in 65.

Redness and swelling (I) were found in 49 infants, 3 of whom produced a positive culture. Grade II reactions were reported in 26, 8 of which were positive. Grade III reactions were found only in 3 infants but in 2 of these 3 cultures were positive.

Incidence according to day of onset after birth. The majority of infants were dis-

Table IV. Severity of ocular discharge

Grade	*Silver nitrate*	*Erythromycin*
I	129 (6)*	49 (3)
II	97 (22)	26 (8)
III	11 (3)	3 (2)

*Numbers in parentheses indicate positive cultures.

Table V. Day of onset

Day	*Silver nitrate*	*Erythromycin*
1	132 (18)*	20 (2)
2	79 (10)	28 (6)
3	8 (2)	5 (1)
4	8	19 (3)
5	7 (1)	6 (1)
6	1	0
7	2	0
8	0	1

*Numbers in parentheses indicate positive cultures.

Table VI. Type of delivery and prophylactic agent used

Type of delivery	*Total number given silver nitrate*	*Total number given erythromycin*
Outlet forceps	1,237 (122)*	945 (42)
Spontaneous	962 (103)	887 (33)
Cesarean section	67 (2)	21 (2)
Breech	54 (5)	50 (0)
Breech extraction	12 (1)	9 (1)
Midforceps	27 (4)	21 (0)

*Numbers in parentheses indicate ocular discharges.

Table VII. Cultures from ocular discharge

Type of bacteria	*Silver nitrate*	*Erythromycin*
Pseudomonas aeruginosa	12	6
Staphylococcus albus	14	4
Alpha Streptococcus	9	4
Escherichia intermedium	1	1
Aerobacter aerogenes	1	0
Hemophilus influenzae	1	0
No growth	206	65

charged with their mothers on the fourth or fifth day post partum. An attempt was made to try to correlate the day of onset of ocular discharge with the material used as a prophylactic agent. The peak incidence of ocular discharge in the silver nitrate group occurred on the first day of life. The next highest incidence was on the second day of life (Table V). In the group given erythromycin, however, the second day of life was the peak period for reactions, with the first and fourth days producing nearly as many.

Incidence according to the type of delivery. The method of delivery in each of the study groups was most commonly cephalic via the pelvic route with outlet forceps or spontaneously (Table VI). A definite correlation between the type of delivery and the incidence of eye discharge could not be made in either group.

Table VII indicates the type of bacteria found by culture of eye discharges in infants of both groups.

In the silver nitrate group 237 infants had varying degrees of eye reactions; 31 of these revealed positive cultures. No growth was found in 206. *Staphylococcus albus, Pseudomonas aeruginosa,* and alpha Streptococcus were most commonly found alone or in combination.

In the erythromycin group, cultures were taken from 78 infants and 13 revealed bacterial growth. No growth was found in 65 infants.

Incidence according to weight. There was no appreciable difference in the incidence of ocular reactions in the group given erythromycin irrespective of weight. In the silver nitrate group, however, the incidence was greatest in the group of infants who weighed from 3,000 to 3,499 grams (12 per cent), with a slightly lower but comparable incidence in groups of infants who weighed from 2,000 to 2,499 (9 per cent), 2,500 to 2,999 (10 per cent), and 3,500 to 3,999 (8 per cent) grams (Table VIII).

DISCUSSION

Two questions were proposed in the Editorial Column of the September, 1952, issue of the JOURNAL OF PEDIATRICS.[3] The first was whether Credé prophylaxis should cease to be a matter of statute and the second was whether there is "any reason to continue by statute and custom an anachronistic preventive method which in itself is not without harmful effects." In January, 1957, the New York Health Department presented a ruling repealing the section of the sanitary code concerning specific prophylaxis for ophthalmia neonatorum, thereby removing the requirement that any prophylactic measure need be taken at birth. In June, 1957,[4] the editors of the JOURNAL urged that the situation in New York be regarded as a scientific experiment and that other communities or states should not rush to change their laws until an adequate period of observation of the New York incident had elapsed.

In April, 1959, the Committee on Medicolegal Problems of the American Medical Association reviewed the status of various state laws requiring silver nitrate prophylaxis.[5] According to their report, all of the states require the use of a prophylactic agent in the eyes of the newborn, and silver nitrate is either permitted or required in each state. In 16 states silver nitrate is required without choice. Because of a lack of unanimity of medical opinion, however, the committee was unable to recommend the use of antibiotics as a substitute or alternative for silver nitrate. Numerous antibiotics have been used as prophylactic agents, i.e., sulfonamides,[9, 10] penicillin,[11, 12, 13] aureomycin,[14, 15] terramycin,[16] bacitracin,[13] etc., with an incidence of reactions (including bacterial or viral infection) ranging from 4 to 10 per cent. Even blindness has been reported from allegedly defective ampules or excessively strong concentrations of silver nitrate.[7, 8]

Mellin and Kent[6] have reported the results of a study in which silver nitrate prophylaxis was discontinued for a 6-month period at the Columbia–Presbyterian Medical Center. The marked increase in the incidence of gonorrheal ophthalmia resulted in the reinstitution of prophylaxis.

There has not been sufficient unanimity of medical opinion in favor of the use of antibiotics as prophylaxis against ophthalmia neonatorum or the discontinuation of any prophylaxis as a substitute or alternative to silver nitrate to warrant a universal change in this public health measure. The change in the effectiveness of antibiotics, the possibility of development of sensitivity, and the increased cost must also be considered seriously.

Silver nitrate has been proved to be a relatively safe and effective medication in the prevention of ophthalmia neonatorum through the years. In the present study only 2 per cent of the 4,292 patients observed developed bacterial ophthalmia neonatorum proved by culture. None of these were gonorrheal in origin. Prenatally, the mothers of these infants were observed carefully and in this type of situation the possibility of a persistent or unrecognized gonorrheal infection is almost completely abolished, which apparently removes the probability of neonatal infection. Of the 2 per cent developing positive cultures, 1.3 per cent were in the group receiving silver nitrate and 0.7 per cent were in the group receiving erythromycin.

Approximately 12 per cent of the patients studied developed ocular reactions of varying degrees; however, cultures of these failed to reveal any evidence of bacterial growth. Nine per cent of the 12 per cent with ocular reactions and negative cultures were in the silver nitrate group and 3 per cent were in the erythromycin group.

Table VIII. Incidence of ocular reaction according to weight

Weights	*Total*	*Reactions*	*Per cent*
Silver nitrate			
500 to 999	1	(0)	
1,000 to 1,499	16	(0)	
1,500 to 1,999	51	(2)	4
2,000 to 2,499	139	(12)	9
2,500 to 2,999	599	(64)	10
3,000 to 3,499	912	(113)	12
3,500 to 3,999	490	(39)	8
4,000 to 4,499	128	(7)	5
4,500+	23	(0)	
Total	2,359	237	
Erythromycin			
500 to 999	1	(0)	
1,000 to 1,499	12	(0)	
1,500 to 1,999	39	(2)	6
2,000 to 2,499	118	(5)	4
2,500 to 2,999	514	(19)	4
3,000 to 3,499	735	(34)	5
3,500 to 3,999	394	(13)	3
4,000 to 4,499	97	(4)	4
4,500+	23	(1)	4
Total	1,933	78	

SUMMARY AND CONCLUSIONS

The results of a study using silver nitrate and erythromycin ophthalmic ointment in 4,292 newborn infants as prophylactic agents for ophthalmia neonatorum have been presented. The following observations were made.

1. Ten per cent of the infants receiving silver nitrate developed ocular reactions as compared to 4 per cent of those receiving erythromycin.

2. There was no significant correlation of incidence of ocular reactions in either group according to month of occurrence, sex, race, type of delivery, type of bacteria, or weight of infant.

3. In 2,359 patients who received silver nitrate, 237 developed ocular reactions. Cultures of these patients with ocular reactions were positive in 31 and negative in 206. Of the 1,933 patients receiving erythromycin ophthalmic ointment, 78 developed eye reactions, 13 had positive cultures, and 65 revealed no growth.

4. Ocular reactions were graded I, II, and III. Five per cent of the silver nitrate group developed Grade I reactions as compared to 2.5 per cent in the erythromycin group; 4 per cent of the silver nitrate group developed Grade II reactions as compared to 1.4 per cent in the erythromycin group, and 0.5 per cent of the silver nitrate group developed Grade III reactions as compared to 0.1 per cent in the erythromycin group.

5. The peak incidence of ocular discharge in the silver nitrate group occurred on the first day of life; in the erythromycin group the second day of life was the peak period, suggesting the probability of a "chemical" rather than an infectious reaction in the silver nitrate group.

Grateful acknowledgment is made to Drs. Florentino Gonzalez, John O'Shea, Francis Fitzmaurice, and David Lee for their assistance in the observations and tabulations made during this study.

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The Hageman factor: determinations of its concentration during the neonatal period and presentation of a case of Hageman factor deficiency

Muzaffer Kurkcuoglu, M.D., and Arthur E. McElfresh, M.D.*

PHILADELPHIA, PA.

IN 1955 Ratnoff and Colopy[1] described 2 adults whose blood exhibited a marked prolongation of the clotting time despite the fact that neither patient had ever experienced hemorrhagic episodes; each had undergone operation without misadventure. Further studies indicated that the factor which was deficient in these patients was different from antihemophiliac globulin, plasma thromboplastin component (PTC), and plasma thromboplastin antecedent (PTA); it did not have the characteristics of the Stuart factor. The deficient factor was named the Hageman factor after the person in whom it was first found to be deficient. The deficiency is inherited but the genetics of its inheritance still are undetermined. Since the original description there have been other reports of the same disorder.[2] In each instance the patients have been free of symptoms despite having coagulation times in vitro as prolonged as those of severe hemophiliac patients. Because of the lack of symptoms and the fact that the disorder is only detected when the coagulation time is determined incidental to other procedures, the exact incidence of the disorder is difficult to determine. It is likely that it is extremely rare, however, since even the capillary coagulation time is prolonged and this test is frequently performed upon children prior to operation.

The Hageman factor has been shown to be the surface activation factor which is responsible for the difference previously observed in the coagulation time of platelet-free plasma when measured in glass and when determined in containers with nonwettable surfaces such as silicone-treated tubes.[3] The in vivo significance of the factor responsible for this marked aberration of coagulation in vitro is unknown; it may be of little importance in normal hemostatic mechanisms. The Hageman factor appears to aid in the initiation of coagulation; when it is deficient not only is the clotting time

From the Department of Pediatrics, Temple University School of Medicine, and St. Christopher's Hospital for Children.

**Address, St. Christopher's Hospital for Children, 2600 North Lawrence Street, Philadelphia 33, Pa.*

prolonged but consumption of prothrombin and generation of thromboplastin are also abnormal.

The purpose of this report is to bring the abnormality to the attention of the pediatrician by presenting a case of Hageman deficiency in a child and to report the results of studies of the content of Hageman factor during the newborn period.

METHODS

The venous clotting time was performed by the three-tube Lee-White method, the prothrombin time by the one-stage method of Quick, and the prothrombin consumption by the method of Stefanini. The thromboplastin generation test was performed according to a previously described modification of the method of Biggs and Macfarlane.[7] Correction studies were performed by adding one-fifth volume of either normal adult serum or the serum to be tested to four-fifths volume of the patient's serum and using this mixture in the thromboplastin generation test with the patient's plasma. The assay was compared with curves prepared utilizing dilutions of pooled normal adult serum. A separate assay with normal serum was prepared on each occasion when the above tests were performed.

Blood was obtained by femoral puncture from a total of 103 normal full-term infants between 1 and 14 days of age. All infants 5 days of age or younger and 7 of the older infants were in the nurseries of Temple University Hospital; the remainder of the infants older than 5 days of age were seen at the outpatient department of this hospital for feeding regulation or other minor problems. None of the infants were ill and none of the nursery group had received vitamin K. The age distribution of those studied is shown in Table I.

Table I

Age in days	*No. of infants studied*
1	14
2	11
3	17
4	12
5	12
6	7
7	8
8	2
9	3
10	5
11	3
12	6
13	5
14	4

CASE REPORT

J. B., a white boy 9 years of age, has always been in good health except for what his mother believes to be an excessive number of upper respiratory tract infections. He was circumcised at 3 days of age without unusual bleeding. He is normally active and has never been considered by either his parents or his physician as being more susceptible to bruises than other children. He has never had swollen joints, large ecchymoses, or prolonged bleeding following cuts.

The patient was admitted to another hospital for tonsillectomy and adenoidectomy. When the routine preoperative determination of the clotting time of capillary blood was found to be more than

Table II

	Patient	*Normal value*
Clotting time (glass)	27 minutes	12 minutes
Bleeding time	3½ minutes	6 minutes
Prothrombin (one-stage)	96 per cent	85 to 100 per cent
Proconvertin	100 per cent	60 to 100 per cent
Platelet count	246,000	Over 200,000
Serum prothrombin	90 per cent	Less than 10 per cent
Clot retraction	Normal	—

15 minutes and a three-tube venous clotting time yielded a result of more than 20 minutes, he was referred to this hospital for study. His physical examination was entirely normal and did not show even the usual pretibial bruises which are so common in boys of this age.

The routine blood counts and urinalyses were negative. The results of studies on coagulation are shown in Table II and Fig. 1. It is apparent that the patient had a prolonged clotting time with poor prothrombin consumption and an abnormal thromboplastin generation test, while his prothrombin time, proconvertin content, and platelets were normal. Mixtures of his plasma with normal plasma did not prolong either the clotting time or the thromboplastin generation of normal plasma. There was, therefore, no evidence of a circulating anticoagulant. The defective thromboplastin generation of the patient's plasma and serum was corrected by the addition of plasma (which had been adsorbed with barium sulfate) or of serum from a normal person, as well as by plasma from a person known to be deficient in PTA. Blood was obtained from the mother, the father, and from the 6-year-old sister of the patient; their plasma showed the same degree of correction of the patient's defect as was observed with normal plasma. The results of the correction produced by the mother's blood is indicated in Fig. 1.

Since it was suspected that the patient might have a deficiency of the Hageman factor, frozen plasma from the patient was sent to Dr. Oscar Ratnoff who very kindly tested it against the original patient who was deficient in the Hageman factor. Plasma from our patient produced no correction of the prolonged recalcification time of plasma from Dr. Ratnoff's patient so that the 2 deficiencies are indeed identical.

Despite our assurance that the patient could undergo his tonsillectomy without fear of bleeding, his mother decided that, inasmuch as he had experienced an unusually healthy winter during the time that these studies were in progress, she would not have

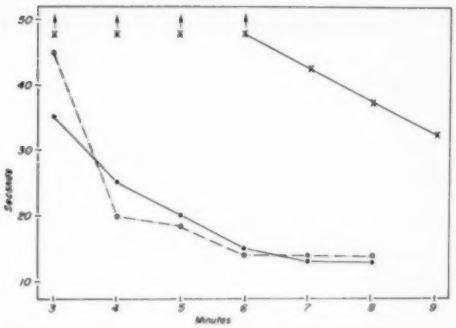

Fig. 1. The solid line with *X*'s indicates the results of the thromboplastin generation test performed with the patient's plasma and serum. The solid line with dots shows the correction produced when one-fifth volume of normal adult serum is added to the patient's plasma and serum; the broken line is the correction produced by one-fifth volume of his mother's serum.

the operation performed. He has continued to be well and has had no hemorrhagic episodes despite playing baseball actively this past spring.

STUDIES OF NEWBORN INFANTS

The corrections produced by infants' serum in the thromboplastin generation tests of both plasma and serum deficient in Hageman factor are compared in Fig. 2 with the correction produced by various dilutions of normal adult serum. It is apparent that the mean content of Hageman factor in the serum of infants is less than 25 per cent of adult serum during the first 6 days of life. The mean concentration in the serum of infants 7 to 9 days of age is between 25 and 50 per cent of adult levels, whereas infants 10 to 14 days of age achieve a concentration which is equal to that of pooled normal adult serum. The mean concentrations from a number of infants, however, do not indicate the extreme variations which were found. These are indicated in Fig. 3 which shows the results of this assay performed with serum from 2 infants each 1 day of age. While one curve is grossly abnormal, the other is similar to that produced by normal adult serum. This

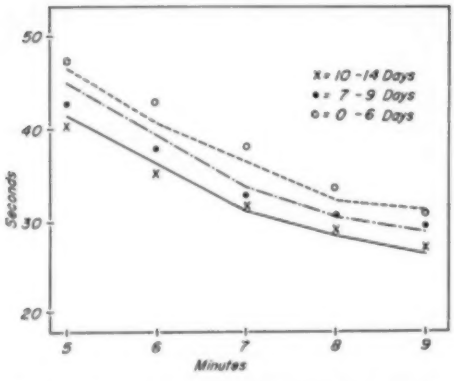

Fig. 2. The mean correction produced in the thromboplastin generation test by the addition of one-fifth volume of normal infant's serum to a test system composed of plasma and serum deficient in the Hageman factor is shown for the age groups indicated. The 3 lines show the curves obtained when one-fifth volume of undiluted adult serum (————) and one-fifth volume of adult serum diluted to 50 per cent (– – – –) and to 25 per cent (– – – – –) concentration, respectively, are added to the same test system.

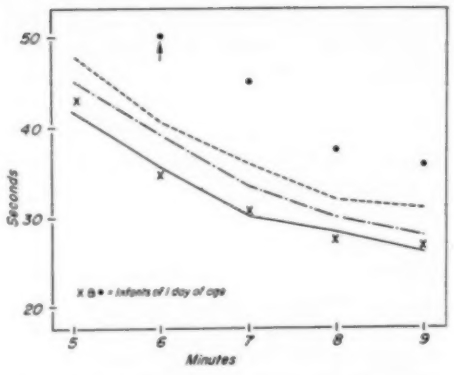

Fig. 3. The results of the addition of one-fifth volume of serum from each of 2 infants upon the thromboplastin generation test of Hageman deficient plasma and serum.
The 3 lines show the curves obtained when one-fifth volume of undiluted adult serum (————) and one-fifth volume of adult serum diluted to 50 per cent (– – – –) and to 25 per cent (– – – – –) concentration, respectively, are added to the same test system.

variation in Hageman factor content was found on all days of life from the first through the fourteenth; for each age studied there were one or more infants whose serum completely corrected the thromboplastin generation of the Hageman deficient system.

DISCUSSION

The origin of the Hageman factor is unknown. Unlike prothrombin Factor VII (proconvertin),[4-6] Stuart-Prower factor,[8, 9] and plasma thromboplastin component (PTC),[7] the concentrations of which are also low during the newborn period, the content of Hageman factor in the blood is not reduced in the presence of severe hepatic disease or does it depend upon vitamin K for synthesis. The low concentration in some infants during the newborn period is probably not related to hepatic insufficiency but may be a manifestation of another enzyme deficiency. Also, unlike the aforementioned coagulation factors which do not reach completely normal levels until 6 weeks of age or more, the concentration of the Hageman factor is normal by 10 to 14 days of life.

The deficiency of the Hageman factor in the newborn should not be considered to have clinical significance since even congenital deficiency of this factor has so far not been associated with spontaneous hemorrhages or with bleeding during operations. With the multitude of "physiologic" deficiencies in the concentration of coagulation factors during the newborn period, it often appears that the blood should not clot at all. However, the blood of infants in the immediate postnatal period usually clots normally in spite of these apparent deficiencies. Fortunately, a deficiency of the Hageman factor need not be considered in evaluating the occasional infant who does bleed excessively during the newborn period.

SUMMARY

A 9-year-old boy with deficiency of the Hageman factor is presented. As in other instances of this deficiency, the patient is completely free of hemorrhagic symptoms despite a prolonged clotting time, an abnormal prothrombin consumption, and an abnormal thromboplastin generation test.

The content of the Hageman factor has been measured during the newborn period and has been found to be low in many infants during the first days of life. Many infants, however, have normal concentrations of the Hageman factor from birth and all appear to achieve normal levels of it by the fourteenth day of life.

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Electrophoretic analysis of serum proteins, lipoproteins, and glucoproteins in healthy newborn infants, older infants, and children in Greece

I. Normal values from birth to adolescence

B. Angelopoulos* and G. Bechrakis

ATHENS, GREECE

THE GENESIS of serum proteins is far from being fully understood. The serum protein of the rabbit embryo at an age corresponding to the middle of pregnancy has been shown by electrophoresis to consist of 75 per cent beta globulin and 25 per cent albumin. Later in pregnancy the concentration of beta-globulin remains at the same level, while the fractions of the other proteins increase rapidly.[1]

Differences in the electrophoretic patterns of serum proteins of the human fetus, the premature infant, and the full-term newborn infant have also been reported, as well as differences between the serum protein fractions of newborn and older infants and of adults.[1-5] The electrophoretic patterns of the serum proteins, lipoproteins, and glucoproteins have become increasingly important in the investigation of many metabolic disorders of infancy and childhood. In comparison with other simpler tests, such as total protein concentrations, albumin-globulin ratio, and the blood sedimentation rate, these procedures are more sensitive.

Determination of serum protein by electrophoresis is now a common procedure in many clinics. Identification of lipoproteins and glucoproteins by electrophoresis is not employed so widely, but the research value of such data is recognized.

This paper presents data on the electrophoretic patterns of serum proteins, lipoproteins, and glucoproteins in normal, healthy Greek newborn infants and children.

From the Institute of Microbiology, Athens University, and the Department of Pediatrics of the General Hospital for Contagious Diseases, Athens, Greece.

Aided by the Department of Clinical Research, Lederle Laboratories, New York, U. S. A.

**Address, Athens University, 3 Alex. Soutsou Str., Athens, Greece.*

MATERIAL AND METHODS

The subjects. One hundred healthy newborn infants, older infants, and children ranging in age from 2 hours to 12 years were included in the study. They were grouped according to age as shown in Table I. Total protein concentrations and albumin-globulin ratios were determined in all subjects by routine laboratory methods.

Determination of electrophoretic mobility of proteins, lipoproteins, and glucoproteins. A sheet of Whatman No. 1 filter paper was cut into 3 equal lengths. A constant serum volume was applied on two of the pieces of filter paper and twice this volume was applied on the third piece. The electrophoretic migration was carried out according to the method of Durrum.[6] The proteins were then stained with bromophenol blue and the lipoproteins with oil red O. The paper carrying the double amount of serum was stained following the technique of Köiw[7] for determination of glucoproteins. The percentage distribution of the various fractions was determined from the dried stained strips by direct reading in a photovolt densitometer model 525. The wave length used was 590 mμ for proteins, 545 mμ for glucoproteins, and 525 mμ for lipoproteins.

RESULTS

Quantative differences between newborn infants and older children and adults were observed (Table II).

Total protein. Values were only slightly lower in newborn infants in the first 3 days of life than in older children and adults; the concentrations then were moderately lower during the ensuing 6 months; thereafter they were within the adult range (Table I).

Total globulin. Concentrations showed only minor variations. They were slightly lower in the first 6 months of life than thereafter (Table I).

Proteins. The electrophoretic pattern of albumin values in the newborn infant during the first 3 days of life corresponded to that of adults. There was a slight decrease during the eighth to thirtieth postnatal days, and thereafter albumin levels were similar to those found in adults. No significant variations were observed in $alpha_1$ globulin values; $alpha_2$ globulin values were increased slightly in newborn infants and these levels were maintained up to the third year and then fell to those of adults. A relatively low level of beta globulin was noted in the first 2 postnatal days. The gamma globulin fraction was at a relatively high level for the first month of life. It then fell gradually during the next 5 months to a level which did not vary significantly during the next 2 or 3 years. Adult levels were attained by 4 to 8 years of age.

Lipoproteins. In newborn infants the electrophoretic pattern is characterized by higher values for alpha lipoproteins and

Table I. Average normal plasma protein concentration values in newborn infants, older infants, and children

Groups	Age	No. of cases	Total protein (Gm./100 ml.)		Albumin (Gm./100 ml.)		Globulin (Gm./100 ml.)	
			Mean	S.D.	Mean	S.D.	Mean	S.D.
A	2 hours to 3 days	11	6.08	0.45	3.86	0.34	2.22	0.27
B	7 days to 30 days	22	5.94	0.44	3.44	0.37	2.50	0.24
C	1 month to 3 months	12	5.85	0.41	3.76	0.48	2.09	0.35
D	3 months to 6 months	14	5.94	0.48	3.77	0.51	2.17	0.18
E	6 months to 12 months	8	6.39	0.52	3.93	0.46	2.46	0.31
F	1 year to 3 years	12	6.25	0.66	3.95	0.53	2.30	0.29
G	Over 3 years	21	6.39	0.72	4.07	0.48	2.32	0.30
—	Adults	—	6.55	0.85	3.90	0.45	2.65	0.24

Table II. Electrophoretic patterns of proteins, lipoproteins, and glucoproteins of newborn infants, older in

		Proteins											
		Albumin (%)		α_1 *globulin (%)*		α_2 *globulin (%)*		β *globulin (%)*		γ *globulin (%)*		*Alph*	
Groups	*Age*	*Mean*	*S.D.*	*Mean*	*S.D.*	*Mean*	*S.D.*	*Mean*	*S.D.*	*Mean*	*S.D.*	*Mean*	
A	2 hours to 3 days	55.0	4.8	4.7	1.1	12.0	2.9	10.1	2.0	18.2	3.1	35.5	
B	7 days to 30 days	50.0	5.0	5.4	0.9	14.6	3.0	13.3	2.2	16.7	3.2	35.9	
C	1 month to 3 months	56.3	4.9	5.3	1.2	11.8	1.9	12.9	2.2	13.7	3.0	34.0	
D	3 months to 6 months	54.6	5.1	4.6	0.9	14.3	2.7	13.5	3.0	13.0	2.7	35.9	
E	6 months to 12 months	53.7	5.2	5.4	1.0	13.3	3.1	13.1	2.7	14.5	2.5	31.7	
F	1 year to 3 years	54.0	5.1	5.0	1.2	14.1	3.1	13.3	2.5	13.6	2.1	28.9	
G	Over 3 years	56.2	5.0	4.9	1.3	9.8	2.0	13.9	2.4	15.2	2.4	28.0	
—	Adults	55.8	4.9	4.8	1.5	10.1	2.8	14.1	2.3	15.2	2.9	29.2	

lower ones for beta lipoproteins (including the chylomicrons, i.e., lipids not migrating in the electric field). This pattern remained unchanged up to the sixth month of life when the adult pattern was attained.

Glucoproteins. In newborn infants the glucoproteins were stained less intensively than were those in adult blood. No significant differences were noted in alpha and beta glucoproteins. The carbohydrates bound to the albumin fraction were increased in newborn infants; in the second month of life they decreased to the adult level. The alpha$_2$ glucoprotein value was lower and that of gamma glucoprotein was higher in the first month of life than were their respective values in the adult. The latter concentrations are attained after the first month of life.

DISCUSSION

Several papers dealing with the electrophoretic patterns of protein and/or lipoprotein fractions of the serum of newborn infants have been published.[1, 4, 5, 8-13]

Glucoprotein determination by paper electrophoresis has been reported in only one paper.[12] The authors probably used a different method or apparatus than we did, since there are differences in the amounts of carbohydrates bound to albumin and gamma globulin as reported in the two studies. Thus a comparison of our data with theirs is not possible.

When we compared our data with those of other authors, we observed that the protein electrophoretic patterns of our infants were in greater accord with those of Italian[10] and Israeli[12] investigators than with those from other countries. Our values for lipoproteins differed distinctly from those reported in Holland.[13] The possibility that these differences can be attributed to variations in prenatal diets should be considered. Dietary patterns in Greece are more like those of the Italians and Israelis than those of the Dutch.

SUMMARY

Total protein determinations and the electrophoretic patterns of proteins, lipoproteins, and glucoproteins were determined in the sera of healthy newborn infants, older infants, and children in Greece.

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...lder infants, and children compared with those of adults

γ globulin (%)		Lipoproteins				Glucoproteins									
		Alpha		Beta		Albumin-bound carbohydrates		Alpha$_1$		Alpha$_2$		Beta		Gamma	
n	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
2	3.1	35.5	5.1	64.5	8.9	25.6	5.1	10.4	3.1	30.7	4.1	18.6	3.1	14.7	3.0
7	3.2	35.9	5.8	64.1	9.1	24.2	4.3	10.0	3.0	34.3	3.8	18.4	3.9	13.1	2.7
7	3.0	34.0	5.9	66.0	10.2	21.4	3.9	11.2	3.8	36.5	5.0	19.9	4.2	11.0	1.8
0	2.7	35.9	6.1	64.1	9.9	21.9	3.8	10.3	2.9	38.3	5.2	18.7	3.3	10.8	2.2
5	2.5	31.7	4.9	68.3	8.8	23.1	4.2	11.3	3.2	35.1	4.7	18.5	3.0	12.0	3.1
5	2.1	28.9	4.4	71.1	10.1	21.4	4.0	8.5	2.4	35.0	4.8	23.4	3.9	11.7	2.3
2	2.4	28.0	4.7	72.0	9.2	20.1	2.9	11.4	3.1	36.8	4.4	20.1	3.2	11.6	2.6
2	2.9	29.2	4.2	70.8	8.9	20.4	3.3	10.8	2.9	37.6	4.1	19.2	3.0	12.0	2.8

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Progeria, a pathologic study

Mamdooh Gabr, M.D.,* Nemat Hashem, M.D., M. Hashem, M.D., A. Fahmi, Ph.D., and M. Safouh, M.D.

CAIRO, EGYPT, U.A.R.

SINCE Gilford[1] introduced the term "progeria" in 1904 fewer than 30 typical cases have been reported. A thorough review of the literature with full description of the syndrome has been made by Thomson and Forfar in 1950[2] and by Gabr in 1954.[3] Several cases have been described subsequently.[4-10] The syndrome is characterized by stunted growth associated with an appearance of premature senility and a normal mentality (the old wizened dwarf). The disease first manifests itself at the end of the first year of life by causing an arrest of growth in both weight and in height, loss of hair, loss of subcutaneous fat with subsequent wasting, and relative enlargement of the joints with limitation of their movement. The face appears small with a receding chin, overcrowded teeth, and prominent eyes with no eyelashes or eyebrows. The skin is thin and the nails are atrophied; the hands with their flexed fingers and enlarged joints simulate the hands of an old person. Skeletal changes, which include thin bones, small clavicles, defective ossification of the skull, and coxa valga, are often present. As the child grows older arteriosclerotic changes develop, and the patient usually dies in the second decade of life of coronary thrombosis. Electrocardiographic changes suggestive of coronary atheroma are usually manifest in older patients.[4, 11, 12] Laboratory data are usually irrelevant, although lately a rise in serum lipids and aminoaciduria[9] have been reported. Tests for endocrine function are usually normal. The disease affects both sexes equally. Since all previously reported cases were sporadic, the disease was not considered genetically determined until the patient to be described was seen in 1954 with her sister who was also affected.[13]

From the Departments of Pediatrics and Pathology, Cairo University, Faculty of Medicine.

**Address, 162 El Tahrir Street, Cairo, Egypt, U. A. R.*

CASE REPORT

Since a full description of the case (A. M.) has been reported,[3] only a brief account of the clinical features will be presented. A. M. was a full-term infant; the delivery was normal. She was the sixth sibling. Her mother and father were first cousins; her younger sister, who also showed typical features of progeria,[13] is still living (Fig. 1).

Alopecia was noted by the mother when the child was 7 months of age. Arrest of growth was reported by the mother after the first year of life with little if any increase in height; there were an associated progressive emaciation and an elderly appearance. Examinations in 1952, when she was 4 years of age, in 1954, and in 1957, at the age of 9 years shortly before her death, were es-

sentially the same. She was dwarfed and emaciated with thin limbs, enlarged flexed joints, and a wizened look. The skin was thin and there were areas of scleroderma and icthyosis, especially over the hands, which with the flexed fingers and the thin and transverse nails, gave them an elderly appearance. There was no subcutaneous fat except in the cheeks and in the pubic area. Her mandible was small and receding with crowded teeth. The clavicles were only palpable for 2 cm. at the sternal end; the anterior and posterior fontanelles were open. The lungs, heart, blood pressure, abdominal viscera, and genitalia were all normal. Investigations including blood cytology, serum calcium, phosphorous, and cholesterol, E.C.G. and urinary 17-ketosteroids were normal except for a persistently elevated erythrocytes sedimentation rate. The 24-hour I^{131} uptake was performed when the child was 8½ years of age and was 42 per cent; the range for our laboratory is 18 to 55 per cent. Roentgen examinations revealed coxa valga, a skull defect at the line of the sagittal suture, normal sella turcica, and normal bone age. The clavicles were only faintly visible at their sternal end. The child was last admitted to the hospital on June 17, 1957, at the age of 9 years for further studies. On Oct. 30, 1957, she suddenly developed a generalized convulsion which lasted 10 hours in spite of sedative measures; it terminated in death.

AUTOPSY

Macroscopic examination. The body, which was markedly atrophic, weighed 9 kilograms, and revealed the following characteristic clinical features: bald scalp, open anterior fontanelle, peaked nose, protruberant eyes, crowded teeth, micrognathia, and a short neck. The subcutaneous fat was minimal with the skin sclerosed over the entire body; this was particularly marked over the lower abdomen and the terminal parts of the extremities where it simulated scleroderma.

On opening the thoracic cavity, the markedly enlarged thymus was obvious. It weighed 32 grams and covered two-thirds of the pericardial surface (Fig. 2). It was fleshy and congested.

The thyroid was fleshy and pale pink. It did not show any gross abnormality although it appeared smaller than normal. It weighed 5 grams. A thorough search revealed no evidence of parathyroid glands.

The heart weighed 85 grams. The pericardium was smooth and contained no fluid. There was no subpericardial fat. The myocardium was firm. The right ventricle was dilated; the wall was only 0.2 cm. thick. The left ventricle was hypertrophied; it was 1.1 cm. thick. The pulmonary valve was 3.4 cm. in circumference; the aortic valve was 4 cm. The cusps over the valves were smooth and of normal thickness and width. The endocardium of the cardiac cavities was thin and smooth. The aorta was not as elastic as usual and was slightly dilated; the openings of the carotid and subclavian arteries were narrowed.

Fig. 1. Patient (A. M.) and her sister (N. M.).

Fig. 2. The thymus gland.

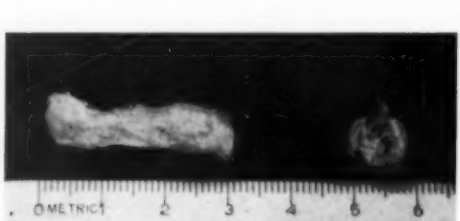

Fig. 3. Fibrous clavicle and pituitary body.

The pleural cavities were free. The lungs were congested, particularly at the base where edema and congestion were evident. Small patches of atelectasis were present over the surface of both lungs, but there was no evidence of consolidation. The cut section presented frothy hemorrhagic exudate, especially from the lower lobes. The pulmonary arteries and their branches were free from emboli. Hilar lymph glands were not enlarged. The larynx and trachea did not show any gross abnormality; the bronchial mucosa was somewhat congested.

The gastrointestinal tract revealed no abnormality; the mesentery and mesenteric vessels were normal.

The liver weighed 380 grams; it was congested, smooth, and soft. Sections showed cloudy swelling. The hepatic veins were patent and portal tracts were not thickened. The gall bladder was empty and appeared normal; its capacity was 6 c.c.

The spleen weighed 50 grams; it was soft in texture and deep pink in color; sections revealed some congestion of the pulp.

The pancreas weighed 30 grams and showed well-developed parenchyma.

The adrenals: both appeared normal; both weighed 5 grams and had well-developed cortices.

The kidneys each weighed 40 grams. They were congested, the cut section showing an extremely congested medulla. The surface was smooth and the capsule thin; the renal pelvis, ureter, and bladder did not appear to be abnormal.

The ovaries were well developed; small cysts were visible on the surface. The uterus and vagina appeared normal.

The brain weighed 800 grams. The meninges were congested, and there was some edema of the brain. The cerebral vessels appeared to be normal. The pituitary body weighed 0.3 gram; no abnormality was noted (Fig. 3).

A great number of samples were taken from the osseous tissue in different areas, which included the skull, the fibrous tissue bands representing the clavicles, the ends and shafts of the long tubular bones, the small tubular bones of the hands and feet and their intervening joints, and the patella and some costochondral junctions.

The clavicles appeared to have been completely replaced by a mass of fibrous tissue 3 cm. long and 0.5 cm. wide at each end; the thickness in the middle was only a few millimeters. Small cartilaginous portions were present at the ends (Fig. 3).

The vault of the skull was very thin (about 2 mm. thick). The anterior fontanelle was patent and measured 3 cm.; it was covered by a membrane (Fig. 4).

The shafts of the long bones were thin and avascular; they could be cut with greater ease than could the bones of children of corresponding age. The joints were normal in appearance.

Microscopic examination. In the pituitary

gland there was apparently a slight increase in the number of eosinophil cells. Patchy mucoid degeneration was present in the eosinophil and the basophil cells but was more marked in the latter. The counts of eosinophilic and basophilic cells (Mallory trichromatic stain) were 45 and 30, respectively. Normally they are 23 to 60 per cent and 4 to 27 per cent, respectively[14] (Fig. 5).

In the thyroid there was some increase in the perivascular interstitial tissue; the vessels showed subintimal fibrosis. The histopathology of the thyroid gland was essentially normal. Small patches of fetal thyroid tissue were seen. In some vesicles the colloid was deficient; the epithelium was high cuboidal. In the adrenal cortex there was normal arrangement of the epithelium. Some mucoid degeneration was seen in the zona glomerulosa under the capsule. The medulla was normal.

Multiple follicular cysts of various sizes were seen in the ovaries. Primordial follicles were abundant. The follicular cysts were abnormally large. There was patchy mucoid degeneration of the stroma (Fig. 6).

The islets in the pancreas were decreased in number, and most of them were quite small. The vessels were thickened. No pathologic changes were seen in the exocrine parenchyma.

In the thymus Hassell's corpuscles were hyalinized, and some of them were calcified. There was hyperplasia of lymphoid and reticuloendothelial structures (Fig. 7).

There was reactive hyperplasia of the reticuloendothelial structures associated with heavy infiltration by mononuclear eosinophils in the lymphoid tissue. The nodes from the mediastinum showed the same changes with less eosinophilic reaction and with evidence of mild anthracosis.

Hyalinization of the central arteries was marked in the spleen. There was also hyperplasia of lymphoid and reticuloendothelial structures.

The liver sinusoids were dilated and engorged with blood. The liver cells were rather atrophic. Glycogen was much diminished.

The myocardium showed large patches of hyaline degeneration and increased perivascular fibrosis. The coronary vessels showed patches of subintimal fibrosis but no evidence of thrombosis. Reduplication of the internal elastic lamina was present in some vessels. The walls of the great vessels showed

Fig. 4. Vault of skull.

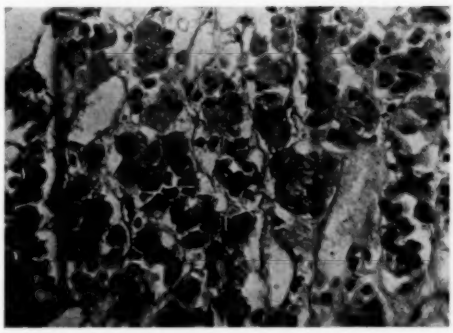

Fig. 5. Pituitary gland. Note the abundance of eosinophils. (×450; reduced ⅔.)

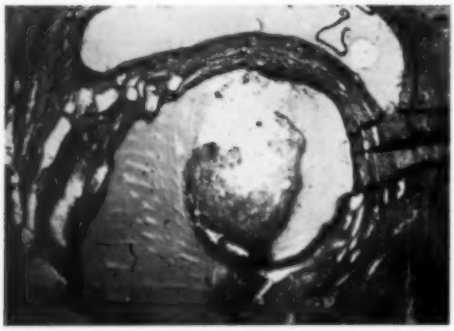

Fig. 6. Ovary showing large Graafian follicle. (×100; reduced ⅔.)

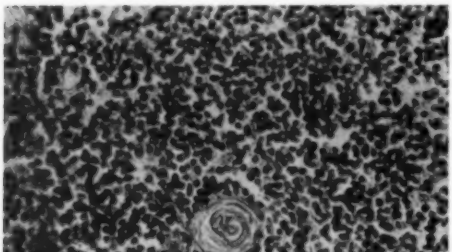

Fig. 7. Thymus showing calcified Hassell's corpuscle. (×100; reduced ⅔.)

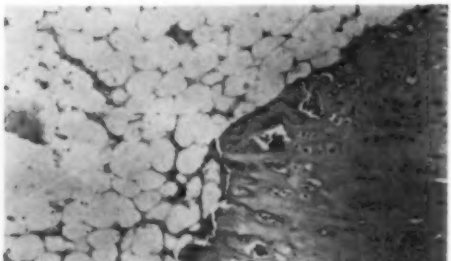

Fig. 8. Epiphyseal plate. Note scarcity of cartilage cells, lack of orderliness of proliferating zone, diminution of thickness of hypertrophic layer, sealing of plate by thin lamella of bone, and lack of metaphyseal trabeculae. (×100; reduced ⅔.)

subintimal proliferation of connective tissue. In some areas the elastic tissue was much decreased or even absent; fraying of this elastic tissue was also seen in some areas.

The lungs were severely congested; many alveoli were filled diffusely with large patches of hemorrhagic edematous material. There was no evidence of pneumonic infiltration.

The kidneys revealed cloudy swelling of the convoluted tubules, and varying degrees of autolysis were present in other tubules. There was marked congestion of the small vessels of the medulla and thickening of the arterial wall.

Abundant endometrial stroma lined by tall columnar mucous secreting epithelium, which formed racimose glandular structures similar to that of the endocervical epithelium was noted in the uterus.

No microscopic pathologic changes were noted in the brain.

The epidermis was thinner than normal, and the basal cell layer was more pigmented. There was dermal and subdermal leukocytic infiltration. The papillae were less prominent than normal. The dermis and subdermis were markedly thickened by diffuse hyaline fibrosis. Many of the hair follicles were degenerated and the sebaceous glands were deficient; sweat glands were fairly normal in number and were surrounded by chronic inflammatory cells. Subcutaneous fat was markedly deficient, being replaced by hyaline fibrous tissue. Elastic tissue was more scarce than usual. The vessels in the hyaline tissue were deficient. The few present had thickened adventitia, and there were perivascular inflammatory cells. Microscopically the articular cartilages of the joints were normal; there was neither the loss of metachromasia nor the fibrillation encountered in degenerative arthritis.

The cortex of the shafts of the long bones was thin, but it appeared denser than normal because of the scarcity and narrowness of the haversian canals, in the formation of new bone. There was also evidence of formation of new bone in the subperiosteum. Otherwise the shafts of the long bones did

not show any morphologic abnormality.

Microscopic examination of the clavicles did not reveal the presence of any osseous tissue. The mass representing the clavicles consisted entirely of fibrous tissue limited by what was once the periosteum.

The epiphyseal cartilage plate of the long bones showed normal appearance of the zone of reserve cartilage. The zone of serial cartilage, however, showed moderate loss of orderliness and of regularity in the enlargement of the cells. The zone of hypertrophied cartilage cells was only 2 or at most 3 cells in depth (Fig. 8). There was partial sealing of the epiphyseal cartilage plate by a thin lamella of bone. Diminution in number and other alterations in the morphologic appearance of the trabeculae of the spongiosa were present.

DISCUSSION

The case presented is the first familial case of progeria to be reported[13] and the seventh case to be autopsied; 5 of the previous 6 were males.[1, 4, 8, 15, 16, 17] As in all previously published cases, evidence of atherosclerosis was present in the aorta and coronary vessels with secondary hypertrophy of the left ventricle.

The endocrine glands, particularly, were examined in an attempt to discover changes that might throw a light on the cause. Macro- and microscopic studies of the adrenal glands revealed no abnormality.

Detailed examination of the pituitary gland was carried out with different stains. The differential cell count of the pituitary gland of our patient was within Rasmussen's normal range.[14] Apart from patchy mucoid degeneration, neither the eosinophils nor the basophils showed any morphologic change. These findings are of particular interest since the anterior pituitary has often been considered to be the site of the basic difficulty. Orrico[15] described a cyst in the pars intermedia. Manchot[16] described diminution in the number of pituitary eosinophils. Talbot and colleagues[17] reported asymmetry of the pituitary gland, although they did not examine the pituitary microscopically. Atkins[4] described a slight diminution in the number of eosinophils, but he commented that such changes were minimal and nonspecific and should not be considered as evidence of a pituitary origin of progeria. The normal pituitary findings in our case support this view.

The thyroid gland did not show any abnormality. In spite of the hypermetabolism reported to be present in progeria by Talbot and co-workers[17] and by Steinberg and associates,[9] no pathologic change was reported in the thyroid of any of the cases that came to autopsy including Talbot's. Furthermore, the normal I^{131} uptake by the thyroid in our case, in contrast to the high uptake reported by Steinberg and associates,[9] is further evidence against the incrimination of the thyroid as an etiologic factor in progeria.

In spite of thorough search, no evidence of parathyroid tissue was found. A review of the previously autopsied cases reveals that the parathyroids were not found in Talbot's[17] case and were small and rudimentary in the cases of Orrico[15] and Manchot.[16] Only 2 parathyroid glands were found in Atkins' case.[4] There was no mention of the parathyroids in Gilford's case.[1] Thomson and Forfar[2] suggested that an etiologic relation might exist between the bone changes and the parathyroids in progeria. Serum calcium and phosphorous concentrations, however, were normal in our case as well as in most other reported cases, indicating that adequately functioning parathyroid tissue must have been present somewhere in the neck, superior mediastinum, or elsewhere.

The thymus was particularly enlarged in our case in contrast to the thin body of the patient. Enlargement of the thymus was also reported in Gilford's and in Talbot's case. A relatively big thymus is particularly interesting in a disease characterized by premature senility, cachexia, and dwarfism. Atrophy of the thymus usually occurs in cachexia, probably through release of corticotropin.[18] The thymus is usually enlarged in cases of acromegaly, the growth hormone having a direct stimulating effect on thymic size.[18] It is thus difficult to explain the per-

sistently enlarged thymus in our case as well as in the above reported cases of progeria.

The ovaries were well developed for the age of the patient, in fact there was a suggestion of premature pubertal changes as evidenced by the large mature follicles and the endometrial histologic changes. Excessive estrin production in animals diminishes the production of the growth hormone by the anterior pituitary.[19, 20] In man, a rare syndrome, leprechaunism, is characterized by dwarfism, cystic ovaries, mental retardation, and other congenital abnormalities.[21] Because of the rarity of autopsy reports of female cases of progeria, it is difficult to evaluate the significance of the changes in the ovaries and genital organs in our case.

The pathologic condition of the osseous system particularly has been studied in our case. Reports on autopsies of other cases of progeria are astonishingly lacking in this respect. As described in the autopsy report, the change in the epiphyseal cartilage is essentially that of a decrease in the rate of formation of endochondral bone. The presence of thin lamellae of bone causing partial sealing of the epiphyseal cartilage plate and the trabecular changes in the spongiosa of the metaphysis are nonspecific changes which occur in many conditions of arrested bone growth including panhypopituitarism.[22] The joint cartilages did not show any evidence of senile or arthritic changes; this observation is in agreement with that of Rosenthal and associates.[5] The changes in the clavicles are most interesting. The clavicles were completely replaced by fibrous tissue. The roentgen changes in the clavicles of the affected younger sister of the patient are of interest in this respect. As reported previously,[13] the younger sister presented a unique opportunity to follow the clinical course of the disease as it developed gradually and before obvious manifestations were apparent. At the age of 9 months the clavicles of the younger sister (N. M.) were radiologically normal (Fig. 9); at the age of 2 years only the central portions of the clavicles were apparent, while at the age of 5½ years the clavicles could not be visualized roentgenographically, apparently because of their transformation into fibrous tissue (Fig. 10). Similar roentgen changes were also observed in the skull.[13] This transformation of the clavicle into fibrous tissue is not observed in any other condition and is apparently due to bone absorption going on in the absence of the formation of new bone. This alteration is limited to membranous bones, the skull, and the clavicles. These skull and cleidal defects have been repeatedly described in progeria,[23, 24, 25] and it has been suggested that cleidocranial dysostosis is an occasional accompanying feature of progeria. These changes, however

Fig. 9. Roentgenogram of clavicles of N. M. at 9 months of age (Sept. 20, 1952).

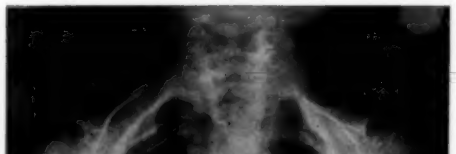

Fig. 10. Roentgenograms of clavicles of N. M. at 5½ years of age (July 27, 1957). Note complete resorption of bone.

are evidently different from cleidocranial dysostosis in which the bony defects are congenital.

The other pathologic features do not merit discussion. Skin changes of scleroderma were very apparent. They have been described in several other cases.[26, 27, 28] The cause of death was not apparent; the patient died during a convulsion. There was no pathologic evidence of the cause or the effect of these convulsive attacks.

SUMMARY AND CONCLUSIONS

A complete autopsy of a girl 9 years of age with progeria is reported. There was no pathologic evidence of an endocrine disturbance as an etiologic factor. The failure to find parathyroid tissue, the mature ovaries, and the enlarged thymus are features worthy of recording, although their correlation with the clinical picture is not clear. The pituitary, adrenals, and thyroid glands were normal. The osseous changes are described in detail. The transformation of the clavicles from bone to fibrous tissue which was observed roentgenographically in the younger affected sister of the patient is a peculiar feature of the disease.

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The characteristic dentition of incontinentia pigmenti

Robert J. Gorlin, D.D.S., M.S.,* and John A. Anderson, M.D.

MINNEAPOLIS, MINN.

INCONTINENTIA pigmenti is a relatively uncommon type of ectodermal dysplasia which occurs principally in females. About 100 cases have been reported to date. It involves the skin, hair, nails, eyes, and central nervous system. It also has what we believe to be rather characteristic dental changes. The changes observed in the skin and the organs are well documented[1-8] and will not be discussed in any detail in this paper.

Either the skin pigmentation is present at birth or the disease is initiated as a vesicular eruption of the trunk which somewhat resembles dermatitis herpetiformis. The vesicles break and become verrucous. This is followed by steel-gray or brownish yellow isolated or confluent streaks, especially over the trunk and extremities. This pigmentation tends to fade within a few years.

Alopecia of the pseudopelade type, atrophic changes in the nails, and ocular changes such as retinal detachment, nystagmus, cataract, strabismus, optic atrophy, pseudoglioma, and retrolental fibroplasia have been noted. Neurological changes include convulsions and central motor disturbances.

From the Department of Oral Pathology, School of Dentistry, and the Department of Pediatrics, School of Medicine, University of Minnesota.

**Address: Department of Oral Pathology, University of Minnesota School of Dentistry, Minneapolis 14, Minn.*

A condition similar to that of incontinentia pigmenti was noted by Naegeli but differs in several respects. There appears to be an associated mild keratosis palmaris et plantaris, diminished sweat gland function, and dominant autosomal inheritance. The teeth are noted to be "bad with yellow spots on the enamel."

A rather careful search of the literature has been made by the authors to ascertain the nature of the dental changes. This information was found in most cases to be missing, inadequate, or poorly documented. Many patients were too young to have erupted teeth. No case report was accompanied by roentgenograms and only 5 were published with clinical pictures of the oral status. In all, 25 published reports and analyses revealed alteration of dental structures: (1) delayed tooth eruption,[6, 7, 10, 17, 19, 21, 22, 30] (2) "pegged" teeth,[7, 9, 10, 15, 17, 22] (3) missing teeth,[3, 5, 7, 8, 10, 11, 15, 17, 18, 19, 22, 31] (4) "malformed" teeth,[4, 7, 8, 14, 16, 21, 22, 29] and (5) familial history of hypodontia.[3, 7, 18, 21]

In addition there was mention of high palatal arch.[10, 21] The term "malformed teeth," frequently used by authors, undoubtedly in many cases referred to conical malformation. Further description of dental abnormality was extremely abbreviated.

We have recently had opportunity to examine 3 cases of incontinentia pigmenti. All

have had dental changes consistent with this disorder. One case was diagnosed prior to our seeing the patient on the basis of available dental roentgenograms.

CASE REPORTS

Case 1. J. S., a 15-year-old white girl, was seen in the School of Dentistry, University of Minnesota, in January, 1959. On the basis of her dental roentgenograms, the tentative diagnosis of incontinentia pigmenti was made.

The following abstracted history and report on physical examination was secured from her family physician and from the pediatrician to whom she had been referred:

The patient, one of fraternal twins, had a normal birth on Jan. 28, 1944, but hospital records indicated that she had diarrhea and a skin condition at birth diagnosed by a dermatologist as epidermolysis bullosa although the skin cleared up within 2½ years. The fingernails were markedly dystrophic at this time. The child gained weight slowly, ate poorly, and had intermittent diarrhea, especially in the autumn, until 7 years of age. Her stools were yellowish with mucus and water. Her family physician saw her for the first time when the patient was 7½ years old. At that time he noted retarded mental development, decreased hearing, congenital absence of several teeth, congenital absence of the nipple of right breast and 3 rudimentary nipples on the left. There was a loss of hair and an unusual distribution of pigment which was located largely on the left side of the body. Because there was development of pubic hair at this age and because there were suggestive cystic areas in the pelvis on roentgenographic examination, a tentative diagnosis of Albright's syndrome was made.

In September, 1951, she was hospitalized because of gastroenteritis and dehydration due to fever. Recovery was uneventful. One month later she was admitted to a school for retarded children. Her intelligence quotient was found to be 71. Blindness in the left eye had been suspected at birth.

Fig. 1. Case 1. J. S., a 15-year-old white girl. Note residual pigmentation about sternum and absence of right breast.

Fig. 2. Case 1. Alopecia of pseudopelade type located at apex of head.

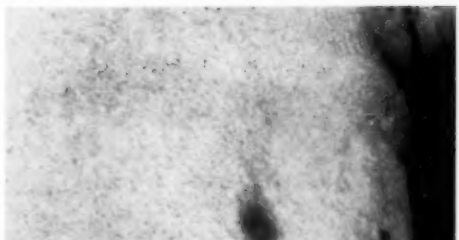

Fig. 3. Case 1. Note supernumerary nipple and residual pigment on outer half of breast.

The patient continued to complain of this intermittently.

Menstruation began at 11 years of age. At this time the left breast was developing but the right demonstrated no mammary tissue. Roentgenographic examination of the pelvis at that time revealed no evidence of cystic bone disease.

The patient has two siblings, aged 19 and 17 years, who are alive and well. Her twin is also normal. There is no family history of unusual teeth or skin disease.

Physical examination. Physical examination revealed a dull girl. The left eye deviated occasionally to the lateral side on forward gaze (Fig. 1).

HEAD. The head had a normal contour; hair was soft, normal and fine with nice curl. A bald spot with a scarred patch of skin at the vertex extended backward for about 3 inches (Fig. 2).

Teeth were missing and had been replaced with dentures. The pharynx was normal with minimal lymphoid tissue. The tonsils were normal. There was lateral strabismus of the left external orbital muscles. The left optic disc was white and atrophied. The retinas were thin with a prominent choroidal pattern and the right fundus was normal. The palate was not of abnormal height.

GENITALS. Hair was in male distribution to the umbilicus. The vulvae, labia, and urethral meatus were normal.

BREASTS. The right nipple was present but there was no breast tissue (Fig. 1). The left breast was normal with a supernumerary nipple above it (Fig. 3).

SKIN. There was a 2 by 3 cm. dark pigmented area over the left lower abdomen and similar pigment under the left axilla.

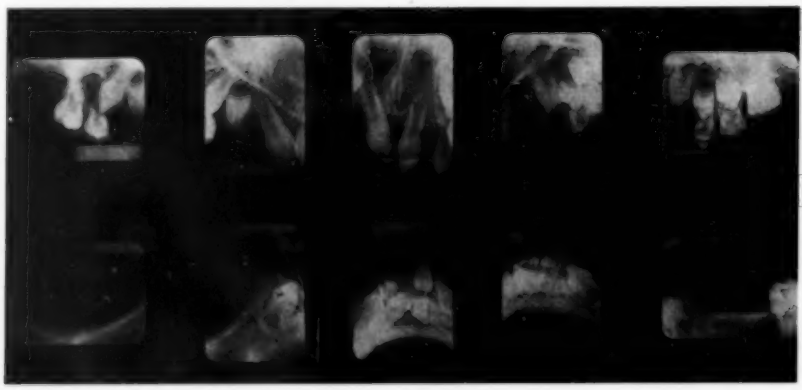

Fig. 4. Case 1. Dental roentgenograms of patient at age 7½ to show effect of incontinentia pigmenti upon both dentitions. Many teeth are missing, impacted, or conical in crown form.

There was depigmented skin diffusely over both thighs and, to a lesser extent, over the lower legs. The fingernails were essentially normal.

Neurological examination. Deep tendon reflexes were equal and symmetrical. Abdominal reflexes were normal. Touch and the sense of position were intact and muscle tone was normal.

Electroencephalogram. This showed moderate diffuse and localized abnormality: (a) excessively slow background, (b) scattered right temporal spikes, and (c) focal right midtemporal spikes in sleep. Lymph nodes, chest, abdomen, and extremities were not remarkable.

Laboratory studies. The hemoglobin level was 13.3 Gm. per cent; white blood count, 5,100; polymorphonuclear neutrophil leukocytes, 55 per cent; and the urinalysis revealed a trace of albumin but was negative otherwise.

The patient was examined at the School of Dentistry for the purpose of removal of her remaining teeth and construction of full dentures. At the time of initial dental examination the following permanent teeth were clinically missing, resulting in generalized diastemas: $\frac{8\ 4\ 2\ |\ 2\ 4\ 78}{8\ 6\ 54\ 1|1245678}$.* There was retention of $\frac{IV\ III|}{I\ I}$. Marked conical shape of the following teeth was noted: $\frac{531|1\ 35}{7\ 32\ |3}$. Impaction of the mandibular central incisors and left lateral incisor was observed. Examination of dental roentgenograms of the patient at ages 5, 7½, and 9½ years revealed similar change in the deciduous teeth, many of which were congenitally missing (Fig. 4).

Case 2. A 10-month-old white female infant was noted to have three "light brown spots" on the right thigh at birth. The spots increased in size and appeared to blister. Within a week the lower lip and feet were involved. The skin darkened and blisters and scales became abundant. Crusts formed and sloughed, revealing more blisters underneath. At 3 months of age numerous wartlike nodules began to appear on the right buttock, arm, fingers, and both legs. Physical

Fig. 5. Case 2. This 10-month-old white girl manifested bullae, verrucae, and linear distribution of pigment along developmental lines of skin.

Fig. 6. Case 2. Note area of crusting and scarification of linear lesion of upper thigh. This is a residuum from more severe inflammatory process in this area.

*Roman numerals refer to deciduous teeth; Arabic numbers, to permanent teeth.

examination at that time was otherwise negative. Laboratory examinations of urine and blood were noncontributory. Biopsy of the pigmented skin revealed "hyperplasia" of the corium and focal hyperkeratosis. Increased melanin was present in the basal layer and in the papillary layer of the corium, and a banal inflammatory infiltrate was noted throughout.

Physical examination at 10 months of age revealed normal growth and development. Pigmentation had increased and involved nearly all areas but the face and neck (Figs. 5 and 6). Five teeth had erupted, three of which manifested the typical changes of incontinentia pigmenti (Fig. 7). Dental roentgenograms of the maxillary and mandibular teeth were taken and revealed the abnormality in other unerupted teeth. The palate was of normal height. Neurological and ophthalmologic examinations were negative.

Case 3. This case has been described by Epstein and associates.[11] In brief review, this 12-year-old girl at the end of the second week of life demonstrated a papular eruption of buttocks and thighs which changed to a bullous variety on the arms, legs, trunk, and face, with a brownish black pigmentation of the skin. Eosinophilia of the blister fluid was marked. The vesicles generally disappeared by the fourth month of life, but bizarre pigmentation and hyperkeratotic plaques developed all over the body. Foci of atrophic alopecia were noted. At 28 months of age the child had convulsive seizures followed by left hemiplegia. A pneumoencephalogram revealed cerebral atrophy on the right side.

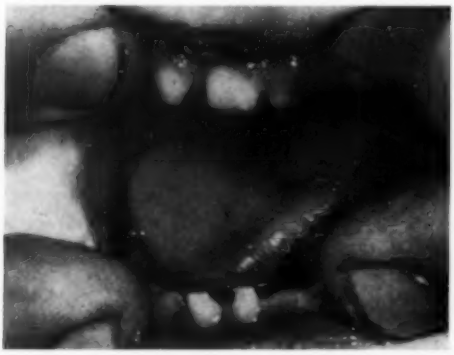

Fig. 7. Case 2. Note that 3 of the 5 erupted teeth manifest characteristic conical crown form. Dental roentgenogram revealed similar changes in permanent incisor teeth.

Fig. 8. Case 3. Dental roentgenogram of patient at age 3 years. Observe the crown form already described.

At 16 months of age, two widely spaced, maxillary, peg-shaped incisors erupted (Fig. 8). By 21 months the left maxillary and mandibular deciduous first molars erupted. Dental roentgenograms taken at 36 months demonstrated absence of deciduous and permanent teeth in the mandibular area.

The patient was seen at 12 years of age on Oct. 8, 1959. History obtained from the mother revealed that no seizures had occurred after 3 years of age; she had been maintained on phenobarbital until 6 years of age.

Physical examination revealed a generally well-developed white girl of average mentality.

Neurological examination. The patient walked with a mild circumduction of the left leg. The left arm and hand were held in a flexed position with a moderate amount of spasticity present in both limbs on the left side. Her reflexes were hyperactive on the left side and there was a positive Babinski

reaction on this side. A sensory deficit to light touch and to double simultaneous stimulation was noted on the same side. Questionable weakness of the superior branch of the seventh cranial nerve was noted on the right side. The neurologist felt that the findings suggested almost complete loss of function of the right cerebral hemisphere.

Electroencephalographic studies revealed marked asymmetry with 4 to 5 per second activity in the right posterior temporal and occipital areas; this abnormality was present only when the eyes were closed. No alpha rhythm was present on the right.

Dermatologic examination. Many larger residual areas of skin pigmentation were present over the legs, buttocks, and lumbosacral area. Smaller areas were noted about the mouth. The nails appeared to be normal. A small area of scarring alopecia was noted at the crown of the head. An adenoma sebaceum–like change was present about the nose and cheeks.

Optical examination. Homonymous hemianopsia of mild grade was noted, the right pupil being somewhat smaller than the left. Reaction to light and accommodation were normal. Nystagmus was marked on right lateral gaze, although present to a lesser degree on the left. The fundi showed cuffing of the vessels at the disc with increased pigmentation in the right retina.

Oral examination. The palate was of normal height. Dental roentgenograms revealed the following teeth present: $\frac{6\ V\ III\ 1}{6\ \ III}\ \Big|\ \frac{1\ III\ 4\ 5\ 6^{*}}{III\ 5\ 6}$. In addition, $\frac{3}{3}\Big|\frac{}{3}$ were present but unerupted. There was a marked diastema between the maxillary central incisors. The deciduous cuspids were conical shaped and identical in form to those seen in Cases 1 and 2 (Fig. 9).

Examinations of ears, neck, breasts, heart, lungs, and genitals were not remarkable.

The patient has 4 siblings: 2 sisters, aged 18 years and 9 years, and 2 brothers, aged 15 years and 2 months. Neither siblings nor any relatives had hypodontia. No history of parental consanguinity was apparent.

DISCUSSION

There apears to be a characteristic dentition present in incontinentia pigmenti. These dental abnormalities affect both the deciduous and the permanent dentition. The changes are: (1) characteristic conical formation of the crowns of the incisors and the

*Roman numerals refer to deciduous teeth; Arabic numbers, to permanent teeth.

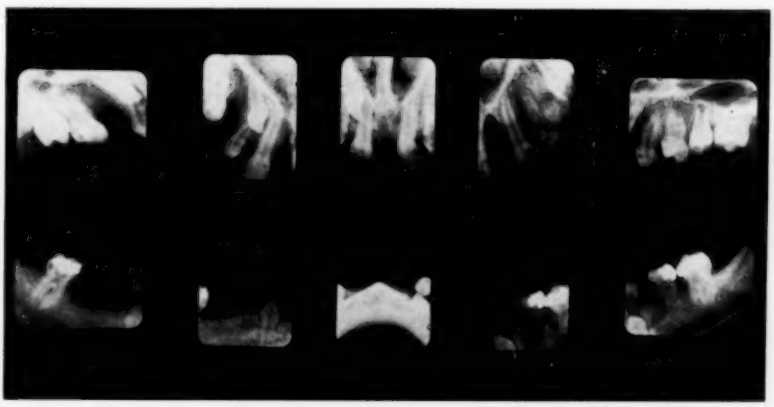

Fig. 9. Case 3. Dental roentgenograms of patient at age 12. Note congenital absence of a number of teeth and typical crown form.

canine and bicuspid teeth with even the coronal portion of molars frequently being altered in that direction; (2) hypodontia or decrease in the number of teeth which, in addition to the tapering form of the crown, causes widespread diastemas; (3) delayed eruption, a common but by no means constant finding. In Case 1 several mandibular anterior teeth were impacted. Until many more cases have been seen, it is impossible to estimate the frequency of this anomaly.

The conical shape resembles somewhat the dental pattern in congenital syphilis and to a greater extent that of hereditary ectodermal dysplasia. In congenital syphilis, the primary or deciduous teeth are almost never involved (rarely is any tooth other than a deciduous molar affected) since the spirochetes are not able to pass the placental barrier until at least the eighteenth week of pregnancy.[23] At this time calcification of the enamel and dentin has already been initiated. The incisors in congenital syphilis, however, are never pointed, the incisal edge being simply narrower than the cervical portion of the crown. Nor are the canines or bicuspids involved. In hereditary ectodermal dysplasia, both dentitions are affected by severe hypodontia and the formation of conical teeth; complete anodontia is common.[24] It should be pointed out, however, that hereditary ectodermal dysplasia of the anhidrotic or hypohidrotic type, unlike that of incontinentia pigmenti, has most frequently a recessive sex-linked pattern, manifest in *males*. The characteristic facies, the diminished sweat gland function, and the absence of pigment should offer no challenge in differential diagnosis from incontinentia pigmenti. Incontinentia pigmenti is certainly, however, a type of ectodermal dysplasia. This is especially well illustrated in Case 1. Hair, skin, nails, tooth crown form (which is dictated by the ameloblastic layer), brain, and eye—all of ectodermal origin—demonstrated faulty development sometime during the disease. The aplasia of the right breast, not described heretofore in this syndrome, is consistent with an ectodermal origin.

It appears entirely possible that the type described by Naegeli in 1927 is a forme fruste of the Zinsser-Engman-Cole syndrome.[25-27]

It is also of interest that the electroencephalographic changes observed in Case 3 may also be seen in agenesis of the corpus callosum.[28]

A high palatal vault mentioned by some authors[10, 21] was not present in any of our cases; neither could a family history of hypodontia be obtained from any of the families.

SUMMARY

Incontinentia pigmenti (Bloch-Sulzberger syndrome) has a characteristic dentition that may aid in its diagnosis. The changes are: marked hypodontia, delayed eruption, and conical crown form of both deciduous and permanent dentitions. Changes similar to those observed in the anhidrotic form of ectodermal dysplasia strongly suggest that incontinentia pigmenti is related.

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Aldrich's syndrome

Report of a case with subperiosteal hemorrhage

Antonio M. Rivera, Captain, USAF (MC),* and

Frederick C. Biehusen, Major, USA (MC)

SAN FRANCISCO, CALIF.

IN FEBRUARY, 1954, Aldrich[1] reported the first case of a sex-linked recessive condition characterized by draining ears, eczematoid dermatitis, and bloody diarrhea. Since then, 19 additional cases of what is now considered a definite syndrome (thrombocytopenia, eczema, and recurrent infection) have been reported.[2, 3, 4] This, the twentieth reported case of Aldrich's syndrome, adds early subperiosteal hemorrhage to the previously reported clinical features.

CASE REPORT

Present illness. A 6-week-old Caucasian boy was admitted to Letterman General Hospital on June 4, 1959. The infant had been transferred from a military hospital in Alaska where a tentative diagnosis of osteogenic sarcoma and idiopathic thrombocytopenic purpura had been made. He was born following an uneventful pregnancy and delivery. No abnormalities were recorded at birth. Petechia-like lesions and the passage of bright red blood via the rectum were noted while the infant was in the newborn nursery. He was admitted to the hospital at the age of 5 days. At this time physical examination revealed multiple petechiae of the skin and mucous membranes. There was no hepatosplenomegaly. The infant remained in the hospital for a period of 35 days during which time partial hematologic work-up, including aspiration of bone marrow, was carried out. Platelet counts ranged between 42,000 and 150,000. The bone marrow was reported as revealing myeloid hyperplasia. He was then placed on corticosteroid therapy. At the age of 1 month, while the infant was still in the hospital, a hard swelling was noted in the upper left calf region which proved on x-ray to be a fracture of the upper end of the tibia. No history of traumatic procedures or accidental trauma could be recalled. Several days later a similar lesion developed in the right calf. X-rays of that site, however, showed no fracture. Roentgenographic examination of the legs a week later revealed radiopaque masses centered on the right upper tibia and left fibula. The orthopedic staff at that time felt that these lesions probably represented malignant bone tumors. The infant then was evacuated by air to Letterman General Hospital.

Family history. The maternal grandmother had 11 children. The first was a boy who died of pneumonia at the age of 4½ months. The second child, also a male, is living and well. The third is this patient's mother and she is well. The fourth, a boy, died at the age of 2 years of meningitis. He had been described to the mother by a physician as being a "bleeder" and at various

From the Pediatric Service, Letterman General Hospital.

**Address, Letterman General Hospital, San Francisco, Calif.*

times had a "skin rash." The fifth and sixth siblings are girls and are normal. The seventh child, a male, died at 2 years of age of "pneumonia and heart disease." The eighth child, a male, and ninth child, a female, are normal. The tenth child, a male, had purpura and subsequently underwent splenectomy. He died at the age of 2 with "cysts in his lungs." The eleventh child, a male, was born several months ago and he also has what has been diagnosed as purpura since birth. This child is currently being seen at the University of California.[5]

Physical examination. The temperature was 99.4° F., pulse, 110, respirations, 28, height, 20.5 inches and weight, 8 pounds, 11 ounces (birth weight, 7 pounds, 2 ounces). He was poorly developed and pale but did not appear to be in acute distress. He had numerous petechiae over the abdomen and chest. The liver was palpable 2 fingerbreadths below the right costal margin and the spleen 1 fingerbreadth below the left costal margin. There was a hard, bonelike mass in the right upper tibial region which measured approximately 3 by 3 cm. (Fig. 1). A similar mass was noted in the left upper fibular region which also measured 3 by 3 cm. There was minimal shotty inguinal lymphadenopathy.

Laboratory data. The white blood count was 13,348 per cubic millimeter; there were 17 neutrophils, 44 per cent lymphocytes, 23 per cent monocytes and 12 per cent eosinophils. The platelet count was 40,000. Blood morphology showed several atypical lymphocytes, polychromatophilic red cells, marked anisocytosis, and poikilocytosis. Bone marrow showed a slight increase in the percentage of early forms in both the myeloid and rubroid series. The M/R ratio was 3.5/1 Megakaryocytes were seen in normal numbers and there were no morphologic abnormalities. There was no iron in the bone marrow. Hematologic work-up showed thrombocytopenia in the peripheral blood and rubroid hyperplasia in the bone marrow. Roentgenograms of the long bones (including review of transferred films) revealed subperiosteal hemorrhage with calcification of the right tibia and left fibula and probably fracture of the upper one-third of the right tibia without evidence of malignancy (Fig. 2).

Fig. 1. Note marked enlargement of the right leg due to the extensive subperiosteal hemorrhage.

Hospital course. The infant had a rather uneventful hospital course and was asymptomatic except for occasional bright red blood in the stools. A right foot drop was noted and thought to be due to peroneal nerve compression by the organizing hematoma in the right tibial area. Gain in weight was satisfactory. He was discharged on June 26, 1959; a diagnosis of hereditary thrombocytopenia was made.

Outpatient follow-up. After hospital discharge, the infant was seen at frequent intervals in the Pediatric Clinic. Both subperiosteal hematomas gradually decreased in size and the foot drop disappeared (Fig. 3). He continued to gain weight satisfactorily and remained asymptomatic except for persistent petechiae and occasional blood in the stools until the end of July, 1959, when a typical eczematoid eruption was noted for the first time over the neck and post auricular areas, with moderately severe seborrhea of the scalp. Subsequently the infant developed recurrent pyoderma and, at the age of 4 months, he had his first episode of purulent otitis media. At this time examination showed right otitis media with perforation and drainage. Since then the infant has continued to have recurring pyoderma, otitis media, and eczema. The platelet counts have ranged between 46,000

Fig. 2. Roentgenograms of lower extremities showing extent and degree of calcification of the subperiosteal hemorrhages.

Fig. 3. Roentgenograms of the lower extremities 3 months later.

and 110,000 per cubic millimeter, the hemoglobin level between 8 and 9 Gm. per cent, and there are monocytosis and eosinophilia. Hepatosplenomegaly has also been a constant finding. His weight on Oct. 9, 1959, was 15.5 pounds. He has been maintained on oral iron and has responded well to specific therapy for the intermittent, recurring furunculosis and otitis media.

DISCUSSION

Aldrich[1] first reported the sex-linked recessive condition characterized by thrombocytopenia, eczematoid dermatitis, and recurrent infections. The latest report[4] brings the total number of reported cases to 19. Huntley and Dees[2] reported 5 cases, Wolff and Bertucio[3] reported on "at least six male members of a Negro family," and Krivit and Good[4] added another 7. Except for those reported by Wolff and Bertucio, all are described in Caucasian infants.

It is felt that the present case is worthy of inclusion in the growing literature of Aldrich's syndrome because of the roentgenographic bone changes which have not been reported in the other cases. The only mention of abnormality of the bone was 1 notation of retarded bone age of an unstated degree.

The roentgenographic findings are not felt to be specific for the syndrome but rather a manifestation of the bleeding diathesis. Since the osseous lesions cleared spontaneously and left no residua, the initial impression of malignancy was not substantiated. The fracture of the right tibia in our patient is not explained well by history and would seem to be incidental. The anemia, eosinophilia, and hepatosplenomegaly described in most of the reported cases were also present in our patient.

In our case, objective clinical findings of the extremities led to the obtaining of x-rays. A better idea of the incidence of subperiosteal hemorrhage may be obtained from routine studies of long bones in children suspected of having Aldrich's syndrome. With thrombocytopenia, a cardinal feature of the syndrome as presently defined, periosteal hemorrhage could be expected more commonly than presently seen.

SUMMARY

A case of Aldrich's syndrome with subperiosteal hemorrhage is presented. Reported cases to date make no mention of bone lesions.

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TROPICAL PEDIATRICS

Diseases of nutritional deficiency of children in South India

A review of some salient conditions

C. Gopalan, M.D. (Madras), Ph.D. (London)*

HYDERABAD, INDIA

OF THE many factors contributing to high mortality and morbidity rates of infants and children in South India, malnutrition is undoubtedly one of the most important. The incidence of diseases of frank nutritional deficiency in the children of the poor segments of the population in this region is distressingly high. Such high incidence of frank clinical malnutrition may be considered to reflect wide prevalence of subclinical malnutrition in the child population. The betterment of the nutritional status of the children in this region calls for an understanding of the major types of nutritional disorders prevalent and of the factors leading to their development. The results of some studies bearing on these aspects, carried out in the Nutrition Research Laboratories, Coonoor (now Hyderabad), over the last 10 years by the author and his colleagues, are reviewed here. This review does not deal with all diseases of nutritional deficiency prevalent among children in South India but with only two major problems: vitamin A deficiency and protein malnutrition. These problems are of such serious magnitude as to overshadow the other nutritional disorders in the region and constitute the major public health problems in the field of nutrition in this area. It is believed that this review may be of more than limited regional interest, considering that malnutrition in children is a global problem common to most underdeveloped regions of the world.

From the Nutrition Research Laboratories, Indian Council of Medical Research, Hyderabad, India.

**Address, Nutrition Research Laboratories, Indian Council of Medical Research, Tarnaka Hyderabad 7 (Deccan), India.*

THE NUTRITIONAL BACKGROUND

Though this review will be primarily concerned with two important diseases arising from malnutrition, it may be justifiable to discuss briefly some studies which throw light on the nutritional background of the infants and children of the poor communities in the region.

Nutrition in pregnancy. Since there is considerable epidemiologic evidence pointing to

the effect of maternal malnutrition on the condition of the infant at birth, it may be useful to review some observations bearing on the dietary and nutritional status of poor mothers in this region during pregnancy. In a study of the dietary intake of a series of 100 pregnant women belonging to the poor socioeconomic group in South India, Pasricha[1] reported the following average daily intake of different nutrients: protein, 44 Gm. (animal protein, 15 Gm.); calcium, 375 mg.; and iron, 18 mg., for a total of 1,875 calories. The dietary assessement in this study was carried out through careful oral questionnaires. Twenty per cent of the infants born to these mothers weighed less than 2.5 kilograms at birth. In a more recent study of the dietary intake of a series of 65 pregnant women belonging to the poor socioeconomic group in Hyderabad, Kalpakam and Venkatachalam[2] observed the following average daily intake of different nutrients: protein, 40 Gm. (animal protein, 6 Gm.); fat, 22 Gm.; calcium, 250 mg.; and iron, 17 mg.; Calories totalled 1,376. The assessment of nutrient intake in this study was carried out through actual chemical analysis of duplicate meal samples. It will be seen from both of these studies that the dietary intake of pregnant women of the poor socioeconomic group in both of these regions of South India is grossly inadequate in regard to practically all the nutrients investigated, with the possible exception of iron. It may be assumed reasonably that the dietary situation in other areas of South India is nearly similar to that observed in these two areas.

In an investigation of the changes in body weight and body composition during pregnancy in a series of 130 women belonging to the poor socioeconomic group in Coonoor and Hyderabad, Venkatachalam and associates[3] observed that the average gain in body weight during the course of pregnancy in these mothers was of the order of 6 kilograms, which is considerably less than the values reported for healthy pregnant women in Europe and America. These studies also indicated that the change in body weight during pregnancy was the sum total of increase in body water, increase in body nitrogen, and decrease in body fat. It is difficult to decide to what extent the relatively low gain in weight during pregnancy in poor South Indian women is a reflection of substandard nutrition.

In a study of the hemoglobin and serum protein levels of a series of pregnant women belonging to the poor socioeconomic group in Hyderabad, Kalpakam and Venkatachalam[2] observed the following values for average hemoglobin and serum albumin levels in the 3 trimesters of pregnancy: first trimester, 12.7 Gm. and 3.31 Gm. per cent; second trimester, 11.8 Gm. and 2.59 Gm. per cent; and third trimester, 11.3 Gm. and 2.41 Gm. per cent, respectively.

Neonatal period. The above studies indicate that the nutritional status of pregnant women of the poor socioeconomic group in South India is far from satisfactory. It would be important to examine how this maternal malnutrition actually is reflected in the condition of the infant at birth. Varkki and co-workers[4] carried out determinations of the birth weights of a series of 500 infants born to women belonging to the poorest section of the population in Coonoor. For purposes of comparison, the birth weights of a series of 200 infants born to women belonging to the well-to-do sections of the population were also determined. A significant difference between the average birth weights of infants in the two groups was observed. The incidence of prematurity (2.5 kilograms at birth) was three times as high in the poor group as in the well-to-do group. The significance of the high incidence of prematurity among the infants born to women of the poor socioeconomic group lies in the fact that prematurity constitutes the most important single factor contributing to the high stillbirth and infant mortality rates in this area.[5] For instance, the rate of stillbirths in the municipal areas of Madras State in 1949 was about 38 per 1,000 births (live and still). The infant mortality rate per 1,000 live births in Madras City in 1954 was 136. Nearly 25 per cent of infant deaths in Madras City in 1954 occurred within 7

days after birth and nearly 38 per cent within the first month. An analysis of the causes of infant deaths revealed the important finding that 73 per cent of deaths of infants below 1 month of age were directly attributable to prematurity.

Jayalakshmi and colleagues[6] carried out simultaneous studies of the blood of mothers and of their newborn infants belonging to the poor socioeconomic group in South India. They found that, in spite of the low hemoglobin content (10.8 Gm. per cent) of the blood of the mothers investigated here, the hemoglobin levels in the infants (17.6 Gm. per cent) were similar to those reported from other parts of the world. The mean serum albumin concentration in the Indian newborn babies, however, was somewhat lower (3.13 Gm. per cent) than the values reported from other regions. It appeared that the low concentration of serum albumin in poor Indian mothers was to some extent reflected in the newborn infants. The serum calcium and serum cholesterol values were, however, apparently normal.

It would appear from these studies that the main effect of maternal malnutrition may be a relatively high incidence of premature births leading to a high neonatal mortality rate. It is also possible that maternal malnutrition may result in a poor storage of nutrients such as vitamin A and iron in the fetus leaving it more liable to develop anemia and hypovitaminosis A in childhood; there is as yet no definite evidence to this effect, however. Varkki and associates[4] found that the birth weights of a series of infants who later developed kwashiorkor were not significantly lower than those of other infants of the same socioeconomic group not developing the disease later, and they concluded that in the development of kwashiorkor, maternal malnutrition and consequent neonatal condition may not be direct contributory factors.

Lactation. An account of the studies on human lactation carried out here has been given elsewhere.[7] Some observations not covered in that review may be mentioned briefly here. Belavady and Gopalan[8] analyzed the milk samples from 191 mothers belonging to the poor socioeconomic group in South India in different stages of lactation for total solids, fats, protein, lactose, vitamin A, thiamine, riboflavin, ascorbic acid, total mineral matter, calcium, phosphorous, sodium, potassium, magnesium, iron, copper, and zinc. The concentration of the proximate principles compared well with the values reported from countries with better diets except that of the vitamins which was lower. After the first month of lactation, neither the stage of lactation nor the parity of the mother seemed to affect the chemical composition of milk significantly. There was no correlation between the iron content of milk and the hemoglobin levels. Samples of milk from women who had become pregnant during the lactation period showed a marked increase in the protein concentration along with a fall in the output. Quantitative studies indicated that the output of milk in these mothers was satisfactory.[7]

The above studies showed that in spite of their poor nutritional status, the breast milk of women of the poor socioeconomic group in South India was apparently adequate in quantity and satisfactory in quality at least in regard to proximate principles. These observations would thus indicate that in the development of disorders of nutritional deficiency of children in the poor communities, maternal malnutrition may not be the major factor; the diets which the children receive after their sixth month obviously play the deciding role.

Childhood. Rao and colleagues[9] carried out a survey of the nutritional status of preschool children in South India. The area covered by the survey was 248,130 sq. miles with a population of 94.8 million. The survey included studies on the following aspects: socioeconomic and living conditions of the families surveyed, general food habits, infant care, feeding and weaning practices, surveys of food intake among infants and young children, clinical examination for signs of deficiency, heights and weights of children, determination of hemoglobin and serum protein levels, and analysis of hospital

records. A total number of 4,536 children were seen in the course of these studies.

From the results of their study, these authors concluded that the probable number of cases of protein malnutrition in children at any given time in the region surveyed might exceed 120,000. Economic poverty appeared to be the most important contributory factor. Even if the entire family income had been spent on food, the nutritional requirements of the family would still not have been met. Customs and traditional practices, adhered to mainly through ignorance, were partly responsible for such faulty feeding habits as inappropriate choice of supplementary foods, avoidance of protein-rich foods, continued administration of purgatives, etc. Infections and infestations appeared to trigger attacks of frank malnutrition in these communities. Nearly 25 per cent of the children examined gave a history of frequent attacks of diarrhea. Prolonged breast feeding of infants was the common practice in the region surveyed. Though the age at which supplementary feeding was initiated varied from locality to locality, there was a striking similarity in the choice of the foods, which invariably consisted mainly of cereal gruels. When compared with the European and North American standards, these children showed a marked retardation of growth from the age of 6 months and beyond. In the hospitals in the urban areas of this region, cases of kwashiorkor constituted 5 to 16 per cent of the total hospital admissions of children.

VITAMIN A DEFICIENCY

Among the clinical manifestations of malnutrition in South Indian children, those attributable to deficiency of protein and vitamin A are the most widespread. While a great deal of attention has been devoted in recent years to the study of the problem of protein malnutrition, the problem of vitamin A deficiency, which is no less important and more easily preventable, has not attracted the same attention.

Gopalan and associates[10] observed that patients with vitamin A deficiency constituted 25 to 30 per cent of all cases of clinical malnutrition in Coonoor and Hyderabad in South India. These authors investigated 319 cases of vitamin A deficiency in Coonoor and 49 cases in Hyderabad. The investigation included, besides clinical examination, a survey of dietary intake with special reference to vitamin A and carotene, estimation of serum vitamin A and carotene before and after treatment, and the determination of the in vitro destruction of vitamin A by the patients' lysed red blood cells.

Incidence and clinical features. The maximal incidence was observed in the age period between 3 and 4 years. Nearly 58 per cent of the subjects were boys and 42 per cent were girls. Of the 319 cases observed in Coonoor, only 23 (7.2 per cent) showed corneal involvement. In the great majority of cases of vitamin A deficiency in Coonoor, the signs were of the milder type involving only the conjunctiva. Nearly 100 of these cases showed the classical Bitot's spots, which were invariably bilateral and situated lateral to the cornea.

An interesting feature was the dissociation between the presence of night blindness and the incidence of visible signs of vitamin A deficiency in the eye. Eighty-five children had night blindness without any other clinical manifestation of vitamin A deficiency, the conjunctiva and cornea being clear and normal. In 113 cases showing conjunctival lesions, no history of night blindness could be obtained even after leading questions. It may be expected that the incidence of night blindness may be modified by such factors as degree of exposure to sunlight, anemia, and the nutritional status with regard to riboflavin and vitamin C.

Keratomalacia observed in 23 patients was invariably bilateral, with one eye being more affected than the other, and included lesions conforming to both the types described by Oomen,[11] namely, "multiple erosions of the conjunctiva leading to mummification of the cornea but without loss of general shape of the cornea" and "colliquative necrosis of the whole cornea leading to shrinkage of the eye ball." From the etiologic viewpoint and

from the response obtained to treatment, there seemed to be no clear-cut distinction between the two types, which appeared to be merely clinical variants of a single disease process. An examination of the monthly incidence of the cases for 5 years in Coonoor failed to reveal any definite seasonal trend. There was no correlation between the incidence of cases of vitamin A deficiency and of respiratory or alimentary disorders.

Of the 49 cases of vitamin A deficiency investigated by these authors in Hyderabad, 33 presented the severe type of vitamin A deficiency involving the cornea. The preponderance of corneal involvement in the Hyderabad series was in contrast to the experience in Coonoor. The age of the subjects did not appear to be a factor in determining the site of the lesion, conjunctival or corneal. In line with the observations in Coonoor, only 14 out of the 49 cases studied in Hyderabad gave a history of night blindness either at the time of investigation or at some time previously.

In another study (Harish Chandra and associates[12]) of the incidence of vitamin A deficiency in Hyderabad, it was reported that while cases of all types of malnutrition accounted for nearly 16 per cent of total hospital admissions of children, cases of vitamin A deficiency accounted for nearly 25 per cent of all cases of malnutrition. The maximum age incidence was again between the third and fifth years. No cases were encountered in infants less than 6 months of age. Sixty per cent of the subjects were males and 40 per cent females. An important finding was that 28 per cent of all cases of vitamin A deficiency observed in this series were cases of keratomalacia. Thus in both the studies reported above, the proportion of cases of vitamin A deficiency showing keratomalacia was much higher in Hyderabad than in Coonoor. The possible explanation for this will be considered later.

A possible objection to the assessment of the incidence of keratomalacia in relation to the total incidence of vitamin A deficiency cases, purely on the basis of hospital admissions, might be that only severe cases of vitamin A deficiency may have been admitted while the milder conjunctival types may have received outpatient treatment. To obviate this objection, Gopalan and coworkers[10] studied the incidence of manifestations of vitamin A deficiency in a series of cases of kwashiorkor in Hyderabad and compared the same with the incidence in a series of kwashiorkor cases in Coonoor. While the incidence of all cases of vitamin A deficiency in the 2 groups was nearly similar (32 to 36 per cent), cases of keratomalacia accounted for only 10 per cent of all cases of vitamin A deficiency complicating kwashiorkor in Coonoor, while they accounted for 62 per cent of cases of vitamin A deficiency in the kwashiorkor series in Hyderabad.

Dietary situation. Surveys of diets were conducted with the use of the oral questionnaire method in cases of vitamin A deficiency[10] and indicated that the intake of carotene in the dietaries of these children was 200 to 400 I.U. while the intake of vitamin A was 90 to 110 I.U. There did not appear to be any striking difference with regard to the intake of carotene and vitamin A between the Coonoor and Hyderabad children. Studies of the chemical composition of breast milk of poor Indian mothers by Belavady and Gopalan[8] had indicated that the vitamin A content of the breast milk of the poor Indian mothers in Coonoor was of the order of 70 I.U./100 ml. It was also found[7] that an average Indian mother of the poor socioeconomic group in this region secreted nearly 600 ml. of breast milk per 24 hours till about the end of 1 year. These observations would indicate that the poor Indian infant receives about 400 I.U. of vitamin A daily from breast milk alone throughout the first year.

An important observation was that while the dietary intakes of vitamin A and carotene were low in the cases of vitamin A deficiency investigated, they were not significantly lower than the intake in other children of the same socioeconomic group not showing signs of vitamin A deficiency.[10] This would suggest that in the development of this deficiency, factors other than the

actual dietaries of the children at the time of the investigation also have to be considered. While it was true that in a number of cases observed by the authors the onset of clinical signs of vitamin A deficiency was preceded by febrile episodes and alimentary disorders, such episodes were apparently no more frequent in children showing signs of vitamin A deficiency than in those of the same socioeconomic group not suffering from the disease.

It appeared that the age at which supplementary feeding was initiated might be an important factor affecting the incidence and severity of nutritional deficiency disorders in children. Mothers in Coonoor invariably started supplementary feeding of their infants by the sixth month while in Hyderabad supplementary feeding of infants was rarely started before the end of the first year.[9, 13] This would indicate that, though at the time of investigation the children in both places had nearly similar levels of carotene and vitamin A intake, the children of Hyderabad were on a vitamin A deficient diet for a much longer time. This might partly explain the higher incidence of severe types of vitamin A deficiency in Hyderabad. Venkatachalam and Gopalan[13] also observed that, apart from vitamin A deficiency, the clinical picture of kwashiorkor in Hyderabad indicated a more severe degree of protein malnutrition than in Coonoor. These authors believe that the late institution of supplementary feeding in Hyderabad may account for the greater severity of the deficiency manifestations in Hyderabad than in Coonoor.

Another important factor which might explain the lack of straightforward relationship between the dietary intake of vitamin A by the children and the incidence of clinical vitamin A deficiency among them is the possible variation in the hepatic storage of vitamin A during the fetal period. In human adults with presumably adequate hepatic storage of vitamin A, deprivation of dietary vitamin A extending over several months was necessary to produce significant depression in serum concentrations of vitamin A.[14] The livers of newborn infants of mothers with presumably adequate intake of vitamin A have been reported to contain considerable amounts of vitamin A.[15] A survey of the dietaries of pregnant mothers in Hyderabad revealed gross deficiency of vitamin A and carotene.[2] The possible effect of such maternal malnutrition during pregnancy in conditioning the infant to vitamin A deficiency in childhood needs further investigation.

It may be pointed out that in the studies carried out here, no case of vitamin A deficiency was encountered in a child with really satisfactory dietary intake of vitamin A and carotene.

Serum vitamin A and carotene. Gopalan and others[10] carried out estimations of serum vitamin A and carotene in their cases of vitamin A deficiency in Hyderabad. For purposes of comparison, similar estimations were also carried out in apparently normal children of the same age group and socioeconomic status in Hyderabad and in cases of kwashiorkor not showing clinical signs of vitamin A deficiency. The estimations were repeated after treatment in a number of cases.

The serum vitamin A levels in the apparently normal children were lower than the average values reported for normal children in other parts of the world. This finding was not unexpected considering that the children investigated were drawn from communities subsisting on unsatisfactory diets. The cases of vitamin A deficiency exhibited considerably lower levels of serum vitamin A and carotene than the apparently normal children. It appeared from the low serum carotene values that defective conversion of carotene into vitamin A was not a factor in the development of the deficiency. The lowest value for serum vitamin A levels observed in the apparently normal group was 45 I.U./100 ml. (average value of 80 I.U./100 ml.). The serum vitamin A levels in the vitamin A deficiency group were below 10 I.U. in 50 per cent of the cases; in the remaining the mean value for serum vitamin A was about 35 I.U./100 ml.

Protein malnutrition and vitamin A deficiency. An interesting observation arising

from the study was that cases of kwashiorkor with no signs of vitamin A deficiency also showed levels of serum vitamin A which were significantly lower than those observed in the apparently normal group. The lowest levels of serum vitamin A were observed in the group exhibiting signs of both kwashiorkor and vitamin A deficiency. It was further observed that treatment of kwashiorkor with a high protein diet without vitamin A supplement brought about a significant increase in the serum vitamin A levels of these cases. On the other hand, the administration of a high protein diet to uncomplicated cases of vitamin A deficiency without kwashiorkor did not produce any significant change in the serum vitamin A level.

The question of the relationship between protein malnutrition and vitamin A deficiency has attracted some attention in recent years. The observations reported here might suggest that protein malnutrition might aggravate vitamin A deficiency. The increase of serum vitamin A brought about in cases of kwashiorkor by high protein diets would indicate that the effect of protein malnutrition may consist in an impairment of the mobilization of vitamin A from the liver. The work of McLaren,[16] on the other hand, has indicated that protein depletion actually delayed the development of signs of vitamin A deficiency in rats. In the study reviewed earlier,[10] it was observed that 6 cases of kwashiorkor which had no signs of vitamin A deficiency on admission developed such signs after a few weeks of treatment with high protein diets devoid of vitamin A. These apparently contradictory observations could be explained if it is recognized that protein depletion may, on the one hand, aggravate vitamin A deficiency by interfering with the absorption of vitamin A and possibly with the mobilization of vitamin A from the liver and, on the other hand, may mitigate vitamin A deficiency by sparing the tissue requirement of vitamin A by inducing growth retardation. The degree of protein depletion may well determine the direction of the net effect.

In vitro destruction of vitamin A. The work of Kon and colleagues[17] indicated the possible presence of factors causing destruction of vitamin A in rabbits and rats. Pollard and Beiri[18] showed that the lysed red blood cells of rats were most active in destroying vitamin A in vitro. The in vitro destruction of vitamin A by the lysed blood cells of cases of vitamin A deficiency and apparently normal controls was investigated by Gopalan and others.[10] In apparently normal children, the in vitro destruction of vitamin A by the lysed red blood cells in 15 minutes was of the order of 28 per cent. Cases of kwashiorkor did not show any significant difference from normal cases in this regard. In cases of vitamin A deficiency with or without kwashiorkor, however, the extent of in vitro destruction of vitamin A appeared to be definitely of a much higher order than in the normal subjects (50 to 60 per cent). After treatment with vitamin A, it was noticed that the abnormally high in vitro destruction of vitamin A in cases of vitamin A deficiency was lowered.

The significance of finding increased in vitro destruction of vitamin A in cases of vitamin A deficiency observed here requires further elucidation from the point of view of pathogenesis of vitamin A deficiency.

PROTEIN MALNUTRITION

The syndrome of malnutrition in children, characterized by edema, dermatosis, diarrhea, and fatty liver is frequently encountered in the hospitals of South India. An exhaustive description of the etiologic and clinical features of this syndrome as observed in Coonoor has been given by Venkatachalam and associates.[19] Venkatachalam and Gopalan[13] have recently reported on the result of study of a series of cases of kwashiorkor in Hyderabad and have pointed to some regional differences in the clinical picture and etiologic background of these cases as between Coonoor and Hyderabad.

The studies on kwashiorkor carried out in Coonoor up to 1955 have been reviewed by Gopalan and Ramalingaswami.[20] The studies on this problem carried out subsequently in South India are discussed briefly below.

Treatment of kwashiorkor with vegetable protein diets. The problem of kwashiorkor in India and other underdeveloped countries is a vast public health problem affecting the poorest segments of the population. While skim milk has been proved to be highly effective in the treatment of kwashiorkor, it is recognized increasingly that skim milk cannot be the practical answer to the problem in most underdeveloped countries. The search for suitable vegetable protein foods therefore becomes important. The choice of the vegetable protein food will be guided by such considerations as cheapness and local availability of the product, its acceptability by the community concerned, and, of course, its nutritive value. Clinical trials with different vegetable protein foods were undertaken by the author and his colleagues with the object of investigating their efficacy in the treatment of cases of kwashiorkor.

Venkatachalam and others[21] investigated the response obtained in a series of 56 cases of kwashiorkor treated with Bengal gram (Cicer arcetinum) and compared the same with skim milk. An important drawback of vegetable proteins is the relative incompleteness of their essential amino acid composition. It should be theoretically possible, however, to overcome this defect through judicious combinations of suitable vegetable protein foods. Srikantia and Gopalan[22] investigated the response of two series of cases of kwashiorkor treated, respectively, with Bengal gram-defatted peanut flour mixture and Bengal gram-defatted peanut flour-defatted sesame flour mixture and compared these to the response obtained earlier[21] with treatment with Bengal gram alone and skim milk alone.

There was no significant difference between the groups in regard to the time of disappearance of edema and changes in weight. The improvement of the associated signs of malnutrition such as crazy-pavement dermatosis, scaly dermatosis, and signs of oral vitamin B complex deficiency was also not different in the groups. With regard to the speed of serum albumin regeneration, however, there appeared to be significant differences between the various diets. The speed of serum albumin regeneration was slower with the Bengal gram diet than with the skim milk. Contrary to expectation, the speed of serum albumin regeneration with the two diets containing the mixtures of vegetable proteins was even slower than with the Bengal gram diet alone. Since the common ingredient in the mixtures, apart from Bengal gram, was the peanut flour, it appeared that the inferiority of the mixtures was mainly attributable to this ingredient. Treatment of a series of cases of kwashiorkor with peanut protein alone yielded the slowest speed of serum albumin regeneration of all the diets investigated.

The possibility of achieving a level of serum albumin regeneration similar to that observed with skim milk with the use of higher levels of the vegetable protein diets and by prolonging the duration of treatment was also investigated by the same authors.[22] It was observed that when the protein level supplied by the vegetable protein mixtures was raised from 60 to 100 Gm. there was a significant increase in the speed of serum albumin regeneration. No such increase in the speed of serum albumin regeneration had been obtained when the protein level supplied by skim milk was raised from 60 to 100 Gm.[23] Evidently there are metabolic bottlenecks which impose a limit on the amount of a dietary protein which can be utilized; this limit may vary with different proteins, being low with a protein of high biologic value like milk and high with vegetable proteins of lower biologic value. It appeared from these observations that the relative inferiority of vegetable proteins as compared to skim milk could be overcome by raising the level of protein in the diet. But it was found difficult to achieve such high levels of protein intake with vegetable protein diets without precipitating digestive upsets. The possibility of using vegetable protein isolates which would help to raise the protein level without unduly increasing the bulk of the food currently is being investigated.

These studies also have indicated that

peanut protein is inferior to Bengal gram protein in regard to serum albumin regeneration in kwashiorkor, and that it may not, therefore, be desirable to use peanut protein as the sole protein source in the management of protein malnutrition.

Hair changes in kwashiorkor. The occurrence of striking changes in the hair has been recognized to be an important though not an invariable feature of kwashiorkor in different parts of the world. Of all the hair changes in kwashiorkor, the discoloration, designated "dyschromotrichia" or "hypochromotrichia," has attracted considerable attention. The incidence of this sign in cases of kwashiorkor would seem to vary in different parts of the world. Available reports would indicate that the African cases of kwashiorkor tend to show this change very commonly. The incidence of dyschromotrichia in cases of kwashiorkor in South India would appear to be relatively less.[19]

Though there have been several clinical descriptions of the hair changes in kwashiorkor, attempts to correlate the clinical features with biochemical changes have been extremely few. Hair protein (Keratin) is characterized by a high content of cystine and arginine and a relatively low content of histidine and methionine. Estimations of these amino acids together with those known to be concerned in melanogenesis, such as tyrosine and phenylalanine, in the hair of patients with kwashiorkor before and after treatment might be expected to provide useful information.

Narasinga Rao and Gopalan[24] estimated cystine, methionine, phenylalanine, tyrosine, histidine, and arginine, and total nitrogen in the hair of apparently normal children and of cases of kwashiorkor with or without dyschromotrichia. The amino acid values for normal hair from well-nourished Indian children were generally in agreement with values reported from other countries. The hairs from cases of kwashiorkor showed a definite decrease in the cystine content before treatment; the cystine content of hair in these cases was restored to normal levels after high protein treatment. When the cystine contents of the brown and black segments of the same hair before treatment were compared, it was noticed that in most cases the black segments had higher cystine content but the values were considerably lower than those obtained for the hair after treatment. There was no correlation between the color of the hair and cystine content. The absence of dyschromotrichia did not signify normal cystine content. These observations would tend to show that the nutritional defect responsible for the discoloration and that responsible for the lowering of the cystine content are not identical, and that a case of kwashiorkor with dyschromotrichia does not necessarily represent a more advanced degree of protein malnutrition than one without this sign. There was not much difference in the nitrogen content of various specimens in spite of marked variations in cystine content. This would indicate a change in the amino acid make-up of hair protein in protein malnutrition. The authors concluded from these studies that it might be unjustifiable to postulate a straightforward relationship between quantitative protein deficiency and dyschromotrichia. Cases of kwashiorkor in South India with a low incidence of dyschromotrichia appeared to be no less severe than cases in Africa among which there was a high incidence of the sign. The cystine content of the hair appeared to be a better indication of the severity of protein malnutrition in a given case than the hair discoloration.

STEATORRHEA IN KWASHIORKOR

Mehta and co-workers[25] conducted careful studies on fat balance in a series of children with kwashiorkor and steatorrhea who had been treated with different diets. On a diet supplying negligible amounts of fat, the output of fat in the feces exceeded the intake. The authors, therefore, concluded that a portion of the fecal fat was of endogenous origin. The administration of glucose was found to aggravate the diarrhea. A wheat diet did not aggravate the steatorrhea as it does in cases of celiac disease. Folic acid had no beneficial effect. Steatorrhea was

found to be more marked with a diet containing peanut oil than with one supplying an equal amount of fat derived from butter. Steatorrhea was found to persist in cases of kwashiorkor long after they had been clinically cured and discharged.

Hematologic studies. Mehta and Gopalan[26] studied the hematologic changes in a series of cases of kwashiorkor and reported that anemia in kwashiorkor may arise from a deficiency of protein, iron, and liver principle. In most cases, a combination of protein deficiency with one or both of the other deficiencies evidently was operative. The pace of improvement in all cases was slow. Obviously in the evolution of the anemia, both deficient supply as well as defective utilization of the concerned nutrients was involved. Pronounced depression of secretion of gastric acid was observed in all cases on admission. After high protein therapy, gastric acid secretion tended to return to normal levels. An interesting finding in this study was that cases of kwashiorkor exhibited eosinophilia within a few weeks of treatment with high protein diet.

Electrolyte changes. Jayalakshmi and others[23] found subnormal serum levels of sodium and calcium in a series of cases of kwashiorkor on admission. After high protein diet treatment, the values rose to normal levels. Serum potassium and magnesium concentrations were, however, within normal limits. The prothrombin time was slightly elevated in these cases on admission. The values returned to normal levels after treatment. These authors also reported that a number of children with kwashiorkor who failed to show a satisfactory eosinopenic response to epinephrine on admission showed a satisfactory response after treatment with a high protein diet.

Follow-up studies. Ramanathan and coworkers[27] had carried out a follow-up study of 100 cases of kwashiorkor in Coonoor. The result of this study had been reviewed earlier.[20] Srikantia and colleagues[28] carried out a more detailed 8-year follow-up study of 15 cases of kwashiorkor. This investigation included histopathologic examination of liver biopsy specimens. Protein deficiency vacuolation of the liver cells, which could be corrected by dietary protein supplementation, was the predominant finding. Evidence of increased fibrous tissue formation was significantly absent. Serum albumin and cholesterol levels appeared normal. This investigation would seem to support the view that there is no direct relationship between the incidence of kwashiorkor and adult cirrhosis in a community.

Pathogenesis of edema in kwashiorkor. The pathogenesis of edema complicating states of malnutrition such as kwashiorkor is not understood clearly. Starling's classical concept whereby physicochemical alterations resulting from the changes in plasma proteins were held responsible for the edema is now recognized as an inadequate explanation. Gopalan[29] observed increased excretion of an antidiuretic substance in the urine of patients with nutritional edema. The response of such patients to a water load test was impaired,[30] and so was that of laboratory animals on low protein diets.[31] A normal liver has been shown to be capable of inactivating the posterior pituitary antidiuretic hormone,[32] this capacity was found to be impaired by low protein diets.[33] On the basis of these observations a tentative hypothesis to explain the pathogenesis of edema was postulated.[30]

Baez and associates[34] showed that the iron-protein complex ferritin can in certain circumstances exert a considerable antidiuretic effect and that this is mediated through the stimulation of the posterior pituitary. Ferritin is stored mainly in the liver and spleen which, under certain conditions, can release measurable amounts of it into the circulation. The presence of ferritin in the blood stream has been reported in such clinical states as congestive cardiac failure, toxemia of pregnancy, hepatic cirrhosis, and the nephrotic syndrome.[35] It seemed important to determine whether the edema of kwashiorkor was also mediated through the release of ferritin from the damaged liver into the circulation.

Srikantia[36] investigated this feature in 6

children suffering from kwashiorkor in Coonoor. Peripheral venous blood was obtained from the patients and plasma separated by centrifugation and assayed for the presence of biologically active ferritin using the rat mesoappendix test.[37] The assays were repeated after the edema had disappeared following high protein diets. Ferritin was demonstrated in the plasma of these cases on admission. Assays repeated after a month of treatment with high protein diet revealed no ferritin in the plasma.

To investigate further the precise role of ferritin in the pathogenesis of edema, Srikantia and Gopalan[38] studied the sequence of changes occurring in induced protein malnutrition in monkeys. While no correlation was observed between serum albumin levels and the increase of the thiocyanate space, there was a striking relationship between the appearance of active ferritin in circulation and the subsequent formation of edema. The increase in thiocyanate space was invariably preceded by the presence of ferritin in the blood. During nutritional rehabilitation, ferritin disappeared from the circulation before the thiocyanate space returned to normal levels. These observations seemed to point to a causal relationship between ferritin and edema in protein malnutrition.

SUMMARY

The foregoing account of studies on nutritional disorders of children in South India has touched on two major problems: vitamin A deficiency and protein malnutrition. Other nutritional deficiency diseases such as scurvy, rickets, pellagra, and phrynoderma are also encountered in the region. Studies on phrynoderma[39, 40] carried out in Coonoor have indicated the role of essential fatty acid deficiency in the pathogenesis of the disease.

From the point of view of prevalence of frank nutritional deficiency diseases, the children between 1 and 5 years of age must be considered the most vulnerable segment in South India. In any rational program of nutritional betterment of the population, this group must receive special attention.

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MEDICAL PROGRESS

Summary Session of Ninth International Paediatric Congress, Montreal, July, 1959

Foreword

THE NINTH International Paediatric Congress was held in Montreal, July 19 to 25, 1959, under the Presidency of Dr. Alan Ross, Physician-in-Chief of the Montreal Children's Hospital and Professor of Paediatrics, McGill University. The scientific program of this Congress, which was carefully and ably organized by a committee under the chairmanship of Dr. J. Harry Ebbs, Professor of Child Health, University of Toronto, and Physician, The Hospital for Sick Children, was extraordinarily basic in orientation and wide-ranging in scope. There were simultaneous sessions much of the time, so that it was impossible for any one individual to take in more than a small fraction of the total program. In order to overcome this difficulty, Dr. Ebbs's Committee decided to close the scientific program with a series of summaries of the major topics covered by the Congress. For those who were fortunate enough to be able to attend this memorable international meeting, the third held in the Western Hemisphere, and particularly for those who could not be present, this summary session is being printed in THE JOURNAL OF PEDIATRICS.

The following persons prepared these summaries: Hematology, Louis K. Diamond, M.D.; Neurology, Richard L. Masland, M.D.; Kernicterus, Bruce Chown, M.D.; Viral Diseases, Joseph L. Stokes, Jr., M.D.; Problems of the Newborn, Clement A. Smith, M.D.; Nutrition, L. Emmett Holt, Jr., M.D.; Surgery, Lawrence E. Pickett, M.D.; and General Summary, Charles A. Janeway, M.D.

Hematology

Louis K. Diamond, M.D.*

BOSTON, MASS.

THE FIRST session was concerned with iron-deficiency anemia. It was pointed out that the world-wide prevalence of iron-deficiency anemia is still increasing. Economic factors, principally diets with a low level of iron and with restricted food intake played an important role in many areas. But even more astonishing was the fact that in the countries in North America and in Europe, where an abundance of food may be obtained, conditions leading to iron-deficiency anemia still persist, chiefly through idiosyncracies in diet and the necessity for educational programs that have not been worked out well. In addition, disturbances in parent-child relationships seem to play a role in the development of some food restrictions that lead to iron-deficiency anemia. This is seen not only in infants but even in children over 3 years of age in this country and elsewhere and beyond that in the adolescent group, particularly in underprivileged populations. The effect of iron deficiency in compromising the function of various heme-containing enzymes and the possibility that this could affect myoglobins and other systems where iron is needed were discussed. It was also pointed out that iron when given parenterally may, in specially indicated conditions, prevent the occurrence of iron-deficiency anemia, particularly in small infants and prematurely born babies. It was also mentioned that nutritional anemia associated with low plasma copper levels exists; whether this is the result of low levels of plasma protein occasioned by a poor protein intake, or specifically a low intake of copper, was yet to be investigated.

At the second session which dealt with the hemoglobins and the hemoglobinopathies, methods of detection of the various hemoglobins, particularly the abnormal ones, the very interesting new method of determining the chemical structure of hemoglobins, and especially the finding that a single amino acid alteration in a chain of 300 amino acids could produce a disturbance as widespread and with as many symptoms as sickle cell anemia were discussed. The physiologic and morphologic conditions, the clinical symptoms, and even the philosophic implications of these abnormal hemoglobins all were discussed. Everyone now knows of the interesting work suggesting that the presence of sickle hemoglobin has a direct bearing on resistance of certain peoples to malaria. The possibility has been raised that some of the other abnormal hemoglobins had some protective value through balanced polymorphism rather than being completely deleterious in action.

At the third session 10 papers on a variety of subjects covering the treatment as well as the symptoms of sickle cell anemia, thalassemia, and some of the other hemoglobinopathies, Vitamin K, hepatic function, and

**Associate Professor of Pediatrics at the Children's Hospital, Harvard University Medical School; Associate Chief of the Medical Services, Children's Hospital Medical Center, Boston, Mass.*

even experimental bone marrow transfusion in animals were presented. Although no new concepts were suggested in these discussions, the knowledge that has been accumulated to date and the latest methods of management of some of these conditions were reviewed.

Nine papers were given at the fourth session, again covering a variety of subjects. Iron-deficiency anemia and its effect on various systems and copper and protein deficiencies were discussed. It was interesting to find that hemorrhagic disease of the newborn, a condition that at one time was considered to be cured by Vitamin K, has reappeared both through more careful analysis of the large number of deficiencies that can occur in the clotting mechanisms of the newborn as well as from the deprivation of Vitamin K. In addition, in many clinics Vitamin K has not been used for quite a long time. The various types of synthetic Vitamin K preparations and their methods of administration were mentioned. Methods of detecting and preventing this old disease that is being seen in increased incidence were discussed. Although some of the subjects of special interest to hematologists were not included in the sessions on hematology, they will be summarized by Dr. Chown in the discussion of hyperbilirubinemia and bilirubin chemistry which is so important in the various hemolytic diseases.

In the fifth session, disturbances of kernicterus and bilirubin in the newborn were reviewed once more. Various discussions of the incidence of hyperbilirubinemia, with or without hemolytic disease in the newborn, particularly in the prematurely born infants, aroused considerable interest. The metabolism of bilirubin which had been covered so well in the sessions on kernicterus was reviewed with regard to the incidence of kernicterus in both full-term and in premature newborn infants. Finally, factors influencing the damage that occurs in infants with erythroblastosis and a review of methods of treatment were emphasized.

In summary, we can once more express gratification with the high caliber of the papers presented, the many new ideas that were brought forth, and the evidence of rapid advances being made, particularly in the fields of the hemoglobinopathies, the chemical characterization of hemoglobins, and the understanding of bilirubin function and bilirubin synthesis in the newborn. These seemed to me the highlights of these 5 sessions.

Neurology

Richard L. Masland, M.D.*

BETHESDA, MD.

AS DR. DIAMOND has indicated, to attempt to summarize this meaty conference is like putting beefstew into a bouillon cube. What is neurology? If one includes in this category those diseases and conditions in which disordered function of the nervous system is the major manifestation, one has outlined a broad field indeed. Within this International Congress, there has been represented almost the whole range of approaches to the causes of disease of the nervous system in childhood. I shall attempt to summarize,

*Director, National Institute of Neurological Diseases and Blindness, National Institutes of Health, U. S. Public Health Service, Department of Health, Education and Welfare, Bethesda 14, Md.

then, by the general area involved.

First of all, one of the most exciting new genetic developments is the discovery of the importance of chromosomal dislocations in their relationship to certain disorders of the nervous system. This has been most strikingly demonstrated by the paper of Barr,[1] which indicates that 1 per cent of the males institutionalized because of defects have female nuclei in their cells. We have gone further now and discovered that in Mongolism there is an extra chromosome. One wonders how many other forms of mental defects may be related to modifications of this sort involving other less clearly recognized chromosomal abnormalities. In respect to the field of inborn errors of metabolism—the next great area of genetic attack—major inroads are being made through screening methods with the use of chromatography, spectrophotometry, electrophoresis, and other similar techniques. We have had papers on phenylketonuria and its dietary treatment, the efficacy of which is still under dispute, although it would appear that the cases treated early are certainly improved by this therapy. We have papers on galactosemia, fructosuria, sucrosuria, and a host of other metabolic disorders being picked up by the above-mentioned techniques. A group of cases reported by Lowe[2] demonstrate abnormalities of the eyes with electroencephalographic changes and pathologic changes in the nervous system, also with abnormalities of tryptophane metabolism. A report by Cochrane[3] reviews the subject of infantile spasms related to abnormalities of pyridoxine.

Another new entity, glycinuria, is reported by Childs and Cooke.[4] These reports lend support to the thesis that many other additional inborn errors of metabolism, with important repercussions on nervous system function, are bound to be picked up with the increasing use of these new techniques. Other specific familial or genetic neurological diseases were described including the important observation by Schaper[5] on the familial trait of sensitivity to light in families of individuals suffering from photogenic epilepsy. This relationship emphasizes the necessity of defining clearly specific forms of convulsive disorders in any attempt to establish a genetic relationship. In respect to epilepsy, a new development reported by Kreindler, Ungher, and Steriade[6] regarding reflex-conditioned epilepsy is of interest. Based on the pioneer work of Pavlov, in relation to the conditioned reflex in certain epileptic conditions, it was demonstrated that electroencephalographic changes can be conditioned. It was also demonstrated that an animal can be conditioned to respond to a sensory stimulus by a response originally produced by direct electrical stimulation of the brain. By proper conditioning techniques they were able to induce a convulsive seizure through the application of a stimulus originally bearing no direct relationship to the initiation of a seizure. One could not help but recall patients whose seizures appeared to be initiated or triggered by some specific incident.

In respect to therapy of convulsive disorders, a group of cases originally described by Gibbs under the term "hypsarhythmia," which are also often termed "infantile spasms," have been found to be amenable to steroid therapy, at least temporarily. Approximately 25 to 30 per cent of such cases respond rather dramatically to steroid therapy.

The observation of Lundström[7] from Sweden on the effects of rubella infection during pregnancy was of considerable interest. Several years ago, a study of the outcome of pregnancy in a group of women in this country reported to the Public Health Service indicated that rubella in the mother during her first trimester of pregnancy was a relatively unimportant cause of congenital malformations. The report of Lundström carried out during an epidemic of measles in Sweden gave quite a different picture. In his large series of cases, the incidence of congenital malformation was very high, especially in those women whose infection occurred during the second month of pregnancy. In the case of therapeutic abortion performed in association with this epidemic a significant number of the aborted fetuses were found to be structurally abnormal.

believe that the discrepancy between these two reports lies in the fact that the second study was carried out during an epidemic, whereas the other was the result of a nonepidemic period. One may question the accuracy of the diagnosis of rubella in sporadic cases during nonepidemic years. It is therefore likely that the observations of Lundström during an epidemic constitute a more valid representation of the true impact of German measles during pregnancy.

It is recognized that many of the neurological diseases of infancy have their origin prior to the time of birth. Our knowledge of these conditions is still grossly inadequate. To what extent are they the result of factors operating during pregnancy, to what extent do they occur as a result of perinatal injury, and to what extent are they attributable to postnatal disease? The ability to recognize a defect of the nervous system at the earliest possible time is obviously essential to define our knowledge of etiology more precisely. A series of 5 motion pictures describing techniques of neurological examination demonstrated that we have come a long way in the development of specific methods of examination for the newborn and small child. There is, however, a great diversity of techniques. On the one hand, there is the outright neurological examination, with its emphasis on specific reflexes. At the other extreme, there is the so-called "developmental examination" with its emphasis on the spontaneous performance of the child in addition to observance of his responses to specified tests of varying complexity. It would seem that some combination of these two approaches would be a healthy development. In the presentation of the neurological examination of the newborn, there was presented the very disturbing situation of an infant who was considered to be completely normal after a thorough neurological examination, yet whose head proved to be transparent when transilluminated with a flashlight. No test is capable of measuring the function of a nonfunctioning organ. If the cortex in the neonate is not an active organ it would seem unlikely that we will be able to test its functional response. It is true, however, that many of the methods of examination, specifically those of muscle tone and presumably those depending on lower reflex mechanisms, are important measures of adequacy in the newborn.

The uncertainty of our knowledge of perinatal factors was emphasized by two papers on the effects of neonatal injury and asphyxia. In a follow-up study by Keith and Gage[8] a series of children suspected of having had birth injuries were subsequently found to be relatively healthy. In a somewhat different approach to this problem, a study of the changes of enamel in a group of children with cerebral palsy and other defects who were presumed to have been injured at birth indicated that the dental abnormality must have taken place months before birth.[9] In other words some or all aspects of the neurological defects may have been the result of a prenatal disturbance rather than of any injury at birth.

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Kernicterus

Bruce Chown, M.D.*

WINNIPEG, MANITOBA

IT IS impossible to summarize in a few minutes the 30 or so papers read in the symposium. First of all there was the tacit assumption that indirect-acting or unconjugated bilirubin is itself the toxic agent that causes the lesion in the central nervous system. This fact is in itself interesting, for such an assumption was being hotly debated only a short time ago; in this latest discussion the assumption was never questioned.

Ever since Holt with Fales at the old Babies' Hospital and Howland's group at Hopkins brought pediatrics and biochemistry together, we in pediatrics have been fortunate in our association with the basic scientists. This happy association was once more exemplified in the symposium. Studies were reported which brought us closer to an exact knowledge of the metabolic pathways followed in the production, conjugation, and excretion of bilirubin and to an understanding of its mode of action as a cytotoxic agent.

Unconjugated bilirubin was accepted as the primary causative agent in the production of kernicterus, but it cannot act upon the nerve cells until it leaves the blood stream and reaches those cells. Studies were reported which suggested that bilirubin linked to or carried by albumin did not leave the blood vessels readily but that if another agent competed successfully with bilirubin for albumin, the frustrated bilirubin then left the blood stream, with the result that the frequency of damage to the nerve cell was increased.

No new clinical methods of immediate application to practice came out of the symposium. That of clinical importance which did result was the strong suggestion that hyperbilirubinemia is in part due to controllable, but presently unknown, factors. The situation seems to me to have a strong likeness to that which prevailed relative to retrolental fibroplasia before the part that oxygen plays in the production of that condition was recognized. We know some factors that increase the frequency of kernicterus in the newborn: large doses of vitamin K to the baby and probably to the laboring mother, some of the sulfonamides given to the baby and probably to the mother, and undefined genetic factors. But there are factors that escape us. It seems to me that here there is an opportunity for the clinician to analyze in detail the methods of care of the newborn, particularly premature infants in his hospital, with the hope of bringing these factors to light. It is quite evident that kernicterus can be prevented in most cases by replacement transfusion. The frequency of hyperbilirubinemia that leads to kernicterus can be reduced by eschewing the use of sulfonamides and large doses of vitamin K. I feel certain that it can be reduced still further through the elimination of other factors, and that we can attain once more the primary object of pediatrics, the prevention of the abnormal and preservation of the normal.

*Professor of Pediatrics, University of Manitoba; Director, Rh Laboratory, Women's Pavilion, Winnipeg General Hospital.

Viral diseases

Joseph Stokes, Jr.,* M.D., Sc.D.

PHILADELPHIA, PA.

IN OPENING the first symposium on viral diseases the chairman emphasized the relative difference between the accumulation of basic knowledge in this area at an exponential rate and the application of such knowledge by the clinical investigator at a much slower rate. It was suggested that the accumulation of basic data could not and should not be diminished, but that a more effective balance be established if possible by improving the amount and quality of effort of clinical investigators who would reach the clinical field via special training and research in at least one basic area for purposes of gaining knowledge, methods, and perspective. The illustration of the splendid diagnostic fluorescent antibody technique developed by Coons was used to indicate the relative lack of application of such methods to clinical problems and the unusual opportunities this still afforded the clinical investigator in the field of viral diseases. In contrast, the rapid application to field work of methods for growing polio viruses in nonnervous tissue cultures by Enders, Weller, and Robbins well illustrates how proper application of such methods by clinical investigators with sufficient funds may initiate major progress in the diagnosis and control of a viral disease.

Dr. Huebner of Bethesda, Maryland, emphasized the exploding nature of virology by contrasting the year 1948, when 60 viruses were known and described in detail, with the year 1959 when at least 160 immunologically distinct viral agents were identified which could infect man. More are being added almost weekly. There are about 45 viruses (zoonoses) transmitted from nature to man; the other viruses are transmitted from person to person. The respiratory viruses now known can explain no more than 35 to 40 per cent of respiratory illness in the pediatric age group. These viruses are chiefly adenoviruses and parainfluenza 1, 2, and 3 (hemadsorption virus II has been renamed parainfluenza 1, hemadsorption virus I has been renamed parainfluenza 3, and the CA, or croup-associated virus, has been named parainfluenza 2). The separation of the respiratory viruses is a problem for the epidemiologist, technologist, and clinician working as a team, and simultaneous "controls" with the same methods for throat, stool, and blood specimens must be arranged. In addition longitudinal studies are usually more productive than cross-sectional ones, although both types are needed.

In studies conducted with Bell, Channock, and Parrott myxoviruses were responsible for 21 per cent of respiratory disease in November, 1959, whereas there were no isolations in June, 1958. In 1 study of 2,043 children 6 per cent had parainfluenza 1 and 3 while in 1,582 controls only 1/2 per cent had these same viruses. The complement fixation tests were less specific than the hemagglutination-inhibition and neutralization tests. All of these respiratory viruses, in contrast to influenza virus, are present at all seasons of the year.

Professor Sven Gard of the Karolinska

*Professor and Chairman Department of Pediatrics, University of Pennsylvania, Physician-in-Chief, Children's Hospital of Philadelphia.

Institute, Stockholm, spoke of viruses of the central nervous system, dividing them into three groups: (1) viruses transferred accidentally from mammalian hosts (rabies, LCM); (2) viruses transferred to man from animals or from man to man by arthropod vectors; and (3) viruses of which man is the natural host, enteroviruses particularly. Professor Gard emphasized that practically all viruses (at least some strains of most viruses) will multiply in the central nervous system and thus there is very little evidence that the term neurotropic is justified, although certain strains cannot grow as well in neural tissue. Howe and Bodian demonstrated that infection with poliovirus could be set up in peripheral nerves, the spread of virus being prevented by transection or chilling of the nerve fiber. Certainly the peripheral nerve plays a major part in the centripetal spread of rabies virus. It appears probable in Gard's estimation that the change in ideas concerning poliovirus spreading mainly by the blood stream is not justified and that invasion by nervous pathways still holds. Very few systematic studies have been carried out indicating a blood-brain barrier. Capillaries in the brain differ from capillaries elsewhere, since in the brain there is not, as elsewhere, a simple filtration of proteins. Thus it is difficult to set up an infection of the central nervous system by intravenous inoculation of virus which easily infects by intradermal or intramuscular injection. There is a possibility that contact infection occurs from infected endothelial cells in the vascular bed, or perhaps from other cells directly exposed to the blood stream. Rickettsioses (although not precisely viruses) infect in this manner. It is possible that captive viruses in white cells are carried across the endothelial lining. In the case of the animal viruses for canine hepatitis and distemper, the lymphatic system seems to be the primary site of virus multiplication and the viruses then pass into the blood stream and are transported by cells. Even in the presence of high antibody titers one can still detect virus in the cells following several washings. Also in poliomyelitis, according to Wenner, virus multiplies regularly in the lymph nodes. Thus it seems possible that the invasion of a particular virus may take place along different pathways. Gard concluded by emphasizing the need for concentrating on prevention and simplified methods of diagnosis, with preferably universal diagnostic sera and the further development of the Coons method mentioned previously.

Dr. F. C. Robbins of Cleveland reviewed newer developments in the viruses of the acute communicable diseases. With respect to measles a new era started in the study of this disease with the demonstration by Enders and Peebles in 1954 that this virus could be grown on tissue cultures of human kidney cells. The cell boundaries disappeared and large giant cells with distinctive inclusion bodies could be readily differentiated by their appearance and by complement fixation tests, with the use of the tissue culture material as the antigen. Following demonstration that the virus would grow in monkey kidney, human amnion, and chick embryo cells, attenuation was obtained by successive cultures in chick embryo tissues, and particularly in chick fibroblasts. Such passage material has been given subcutaneously to susceptible children by Katz and Enders and by others and has produced measles similar to the disease as modified by the usual dose of gamma globulin. No virus was obtained from the throat or from the blood in this modified disease. The antibodies produced were similar in titer to those produced by the natural disease. There would seem to be some need for the attenuated virus as a vaccine (formalized virus has not been fully tested) unless the disease now occurring from the attenuated virus results in encephalomyelitis. As yet there has been no evidence of this in the few studies available. The data relating to the persistence of antibody are too meager as yet to be of value. In isolated parts of the world, such as in island populations or in the South African mines, such a vaccine might be of the greatest importance.

With respect to rubella, if infection of the pregnant mother occurs in the first trimester of pregnancy the chance of anomalies in her

infant is 10 to 20 per cent. The virus has only been transmitted to monkeys on rare occasions, possibly owing to their inapparent infection under the usual conditions of captivity. Further efforts should be made to infect monkeys only recently separated from their native habitat. Recent epidemics caused by Coxsackie and Echo viruses have been accompanied by rashes difficult to distinguish from rubella. It is probable that gamma globulin differs considerably in its level of antibody for rubella, although no method is presently available for testing this. Apparently the administration of gamma globulin intramuscularly has afforded considerable protection in certain outbreaks, particularly when the gamma globulin was obtained from convalescent cases as did Gray Anderson in Australia. Large doses of 15 to 20 ml. of gamma globulin are usually recommended for pregnant women exposed to rubella; however, protection cannot be assured. The question has not been answered as to whether the mother with a history of rubella may still transmit the virus to her fetus if she is again exposed.

With respect to varicella, Weller and Stoddard in 1952 grew the virus in human embryo tissue cultures and in other human and monkey tissues. The vesicle fluid of acute cases proved to be the best source of the virus; the crusts were not a good source. Inclusion bodies similar to those described many years ago by Tyzzer appeared within the nuclei of the cells and contiguous cells passed the virus from one cell to the next—a process which could not be stopped by an antibody. Thus for passage it was necessary to use whole infected cells since the virus could not be passed by using the fluid phase of the tissue culture. These workers also demonstrated that varicella and zoster are different manifestations of the same viral agent, varicella apparently being the first generalized manifestation and zoster the localized reactivation or reinfection in a relatively resistant person, as in herpes simplex. In one case of zoster the virus was found in the spinal fluid thus indicating invasion of the central nervous system.

Dr. A. B. Sabin of Cincinnati described the present status of field trials with oral, live attenuated poliovirus vaccine. Virus strains of the three types were selected for low neurovirulence, absence of viremia, good multiplication in the intestinal tract, and good immunogenic effect. Optimal progeny from single particles were then obtained by the plaque technique of Dulbecco. The attenuated viruses spread to contacts in a manner comparable to natural virus. Ten successive passages of attenuated virus were carried out in susceptible children by Prof. A. A. Smorodintsev of Leningrad without evidence of major change in neurovirulence. The safety of such vaccine for the recipients and the community cannot be determined by small trials, but only by field trials on a large scale. Countries with large nonimmune populations were chosen and also populations in which other viral infections of the intestinal tract would not be likely to interfere as they are apt to do in tropical or subtropical areas. Preliminary studies were conducted in Mexico, Singapore, Czechoslovakia, Leningrad, Estonia, and Latvia in about 1/2 million persons, mostly children, and small groups were studied in the United States, Holland, Sweden, England, and Chile. Up to July 15, 1959, under the direction of Professors Chumakov and Smorodintsev 6,374,000 children in the Soviet Union received the oral, live attenuated vaccine of the three types with no illness resulting from the vaccine as far as could be determined. About 50 to 60 per cent of the children were vaccinated in Estonia, Latvia, Byelorussia, Lithuania, and Moldavia; the remaining ones served as controls. If paralytic poliomyelitis had occurred from this vaccine one would have expected at least 5,000 cases for every 1 million nonimmune persons. By July 15, 1959, the vaccine appeared to be safe and the usual seasonal increase in disease had not occurred.

Dr. H. Koprowski of Philadelphia described vaccination against poliomyelitis with live attenuated virus in which he reviewed the history of early studies of such vaccine, starting Feb. 2, 1950, with the first report

presented in March, 1951. The early studies demonstrated: (1) that virus spread from vaccinated persons to nonimmune ones; (2) that in 6 serial passages of the virus from child to child, there was no increase in neurovirulence for monkeys; (3) and demonstrated the interference in the intestinal tract between two strains of virus. The minimal infective dose, the different means of oral administration, and the size of the dosage were also studied. Infection of infants possessing transplacental antibodies was accomplished by oral vaccination irrespective of the height of antibody titers in the infant's blood. The younger infants below 60 days of age required somewhat larger doses of virus to secure infection. The vaccine virus did not spread in the nursery but did spread readily among children who were very active. The children have maintained adequate levels of antibody against the attenuated viruses used, even up to 9 years postvaccination. Dr. Koprowski also conducted the first large field trial in the Belgian Congo in accordance with which Chumakov and Smorodintsev fashioned their field trials in the Soviet Union mentioned above by Sabin. In continuation of the field trials Koprowski arranged for oral vaccination of about 850,000 children in Poland. No evidence of paralysis has occurred in these children.

Doctors C. H. Stuart-Harris, S. K. R. Clarke, R. Sutton, and D. Hobson of Sheffield discussed the clinical significance of the "new" respiratory viruses. Their introductory remarks were well covered in Dr. Huebner's review above of respiratory viruses. Para-influenza 3 (hemadsorption virus Type I) was placed in the nasopharynx of 15 volunteers at Salisbury, England, 4 of whom developed "common colds." Para-influenza 1 (hemadsorption virus Type II) also caused "common colds" in volunteers at Salisbury. These viruses were rarely recovered from normal children.

Doctors K. Nakamura, T. Watanabe, T. Kitayama, K. Kamimura, Y. Masuda, A. Ishakawa, T. Kinoshita and, K. Yokoi of Tokyo reviewed clinical and virologic studies on acute respiratory diseases of children in Tokyo. Psittacosis was first described in Japan in 1956. Among 260 respiratory infections an adenovirus was confirmed as the etiologic agent in 6.5 per cent; 11 per cent were due to Type 3, Coxsackie A (herpangina) in the summer of 1955. In another group of children with minor respiratory illnesses 15 per cent had a Coxsackie A virus while in a third group of apparently healthy control children, 7.9 per cent had a Coxsackie A virus. Other viruses isolated in Japan were Echo virus (Type 6), influenza A and B, and Sendai (para-influenza 1).

Dr. H. G. Gramblett of Iowa City discussed the relation of infection with certain Echo viruses to respiratory illness in an orphange in Washington in February to July, 1956. Fever, coryza, pharyngitis, and loose stools with mucus were present in 6 infants 5 to 14 months of age. With monkey kidney cell tissue cultures he was able to obtain Echo virus Type 20 more frequently from the stools than from the throat and all 6 had a rise in neutralizing antibodies to this virus. In Iowa 400 sera were studied and in 35 per cent of adults and in 5 to 26 per cent of children neutralizing antibodies were found to Echo virus Types 8 and 20. When antibodies to either of these viruses were below a titer of 1:16 they did not pass the placenta to the infant and in a number of cases maternal antibodies as high as 1:32 or 1:64 did not pass the placenta.

Doctors C. C. T. Vinh, P. Satgé, and M. Lelong of Paris provided the first description of pulmonary lesions in 2 fatal cases (infants, 6 months and 2 years of age, respectively) of adenovirus Type 7, which were entirely similar to those with inclusion bodies previously described by Goodpasture before the exact virus etiology was known. Goodpasture 20 years previously had termed the disease "inclusion body pneumonitis" and had mentioned the eosinophilic inclusions in the early stages of the disease and the basophilic inclusions later in its course.

Dr. J. Dombrovskaia of Moscow reviewed an influenza A_2 outbreak in newborn infants ranging up to 3 months of age. The symptoms were extremely severe with anorexia,

ileus, bradycardia, edema of the face, bronchopneumonia, otitis media, and many petechiae. The successful treatment consisted of mother's blood, gamma globulin and immune and hyperimmune sera, administered intravenously and intranasally.

Doctors S. Kibrick, C. Martin, S. V. Kevy, and J. F. Enders described 77 cases of Echo 9 disease occurring in Boston in 1958. Over 70 additional cases in this area were identified by others. The peak was in August. They also found Coxsackie viruses B3, B4, B5, and the 3 poliovirus types. Echo Type 9 was easily recovered from the spinal fluid, throat, and stool during the first week of illness but only from the stool during the second week. The incubation period was 2 to 15 days with a median of 6 days. One newborn infant became ill immediately after birth and had a rash at 5 days. Echo Type 9 was obtained both from the mother's and from the infant's stool. Many had a rash, aseptic meningitis, or both. Two-thirds had meningeal signs. Less common symptoms included pain on eye motion, photophobia, vertigo, abdominal pain, and pains in legs (unable to bear weight). Three had signs of more extensive involvement of the central nervous system including drowsiness, slurred speech, ataxia, impaired co-ordination, and nystagmus. One 18-year-old patient had loss of bladder and bowel tone with a combined Echo 9 plus Coxsackie B4 infection. The rash in Echo 9 infection, which was rubelliform, decreased in frequency with age and almost always involved the face. In more than half of those with rash, it was generalized; in the others the face, neck, and trunk or extremities were involved. Rarely it was biphasic. In 8 patients it had a petechial component. A grayish enanthem was present during the first 2 days in 3 cases. The spinal fluid varied from no cells to 2,000 or more, the highest count being 3,700 but the median count was 100 to 199 cells. Spinal fluid protein (median level) was 45 mg. per cent. Virus was recovered from the spinal fluid in 1 case with no cells and in one with 2 cells. By general agreement Echo 9 virus is now accepted as Coxsackie Group A Type 23.

Doctors M. C. Lepow, D. H. Carver, H. T. Wright, Jr., and F. C. Robbins of Cleveland described an extensive study from 1955 to 1958 on the etiology and clinical studies in aseptic meningitis. Poliovirus was not important after 1955. Coxsackie virus B_5 was present from 1955 to 1958. Echo 9 virus was present in 1957 and 1958, but without exanthem, and was the most easily recovered virus. In 1957 recovery of the virus was obtained in 43 per cent whereas the virus was recovered in only 7.5 per cent of the controls. A better method of recovery is needed, since from about one-half the patients, and these the more severe ones, no virus was obtained.

Dr. D. M. McLean of Toronto after reviewing the types of virus appearing in various years, described Coxsackie B_5 infection in 33 patients from whose feces virus was recovered. In children 4 to 12 years with Coxsackie B_5 loud pericardial friction sounds had been heard as well as pleural rubs. One patient had constrictive pericarditis and died after operation. In 11 other cases severe abdominal pain was the presenting symptom. In 1956 40 per cent of the cases with Echo 9 virus infection had a rubella-like rash.

Dr. I. Archetti of Rome who was introduced as the father of Echo 9 virus, described the isolation in monkey kidney tissue cultures of a virus which apparently caused paralysis in suckling mice only after tissue culture passage. This virus was considered as a new type of the Coxsackie A Group, but according to the Committee on Enteroviruses belongs to Type Echo 9.

Dr. A. Steigman of Louisville in a paper on "Clinical Paralytic Poliomyelitis Due to Coxsackie Virus Group A Type 7" stated that other enteroviruses than poliovirus are now known to cause neuronal disease and paralysis. In a paralytic child Coxsackie B_5 virus was isolated in 1952. Also in 1952 Echo 2 virus caused fatal bulbospinal paralysis. In 1956 a 3-year-old child with Coxsackie A 7 had paralysis; thus viruses other than Echo 9 produce paralysis and rashes. The Russians have seen many cases of paralysis from Coxsackie A 7; their findings have been confirmed.

Doctors F. Buser and M. Schar of Bern described their studies with Koprowski attenuated viruses Types 1 and 3 in 196 children (triple negative). Type 3 was given orally 1 to 2 months after Type 1. Blood samples were obtained before and after feeding. Stool excretion remained positive in about one-half of the children after 30 days. No illness occurred after administration of the vaccine. In 34 children (previous Salk vaccine), Type 1 antibodies rose to 1:200 after live Type 1 vaccine; in 196 children (no previous Salk vaccine) Type 1 antibodies rose to 1:200+ after live Type 1 vaccine; 39 children with previous natural immunity failed to excrete virus after Type 1 living virus vaccine, and in 46 children (previous live virus Type 1) Type 3 antibodies rose to 1:200 after Type 3 living virus vaccine. Antibody titers were good after feeding Types 1 and 3 live poliovirus vaccine if the child had no previous antibody. The monkeys injected with passage virus had shown no paralysis after intrathalamic injection and no histologic lesions were found.

Doctors G. H. Stuart-Harris, S. K. R. Clarke, A. P. Goffe, and E. G. Herzog of Sheffield carried out a small study on 14 boys with Sabin's Type 3 vaccine. Viruses from the first and last positive stools of the study period were obtained. The passage virus from the stools of 1 child in a dose of 8,000 infection doses produced paralysis in 2 or 3 monkeys on intrathalamic injection thus indicating increased neurovirulence of the virus, although the number of observations was hardly adequate to draw any conclusions.

Doctors H. L. Hodes, R. Berger, M. M. Hevizy, and H. D. Zepp of New York described a method for preparation of radioactive poliovirus and its use in a filter "blocking" antibody test. Filter paper is suspended in a solution of poliovirus which spreads up the paper in a regular, reproducible manner and when the virus is "tagged" with P32 its degree of spread against immune sera is readily determined by means of a counter. This method can be used by either diluting the virus solution with the serum titer constant or vice versa. Neutralization tests and the paper blocking test are in good accord. For example 135 of 138 tests gave the same results for the neutralization and the paper blocking tests. The method is simple, saving time and materials, since only 1 drop of serum and 1 tissue culture tube are required for each test.

Doctors M. L. Lepow, D. H. Carver, H. T. Wright, Jr., and F. C. Robbins of Cleveland described the immunologic potency of commercial poliomyelitis vaccines in young children without prior polio antibody and the persistence of vaccine produced antibody. This was a cooperative study with 4 commercial vaccines, which varied from a minimal level of potency up to good potency. In Cleveland a fourth vaccine injection was given. The vaccines were supplied by Dr. Roderick Murray. With 240 infants "triple negative" at 6 months to 2 years of age, the first 2 doses were given 1 month apart. Blood was obtained 1 month after the second dose, the third dose was given 7 months after the second one, and the fourth dose 18 months after the third one. The antibody response was poor after 2 doses, whereas all but 7 had good responses after the third dose. The antibody rise was best to Type 2, poorest to Type 3. After the fourth dose the response, with 1 exception, was quite good even to Type 3. Gordon Brown of Michigan had similar results using cases from an original study of T. Francis and others.

Dr. O. D. Fisher of Rochester, England, described a trial of vaccination against poliomyelitis with live virus vaccine and subsequent determination of the resulting immunity. Together with Dr. George Dick of Belfast a study was made of the TN and SM strains of poliovirus oral vaccine in 21 adults, 155 children, and 10 infants. Minor illnesses occurred about equally in the vaccinated persons and in a group of controls. In the next 4 months there was no evidence of paralytic poliomyelitis in the community. Serologic studies 7 weeks after SM revealed a drop in antibody titer similar to that after commercial vaccines. Surveillance of contacts and of their contacts was difficult.

Dr. M. M. Da Silva of Washington reviewed poliomyelitis vaccination programs in South and Central America, viz., Colombia, Nicaragua, and Costa Rica. The vaccine used was from Dr. H. Cox and included Type 1 (SM log 4.7), Type 2 (MEF1 log 4.9), and Type 3 (Fox, log 5.2), 0.5 ml. of vaccine was given from dropper bottles. Only 8 per cent of the children lacked antibodies to Type 2, and only 20 per cent lacked antibodies to Types 1 and 3. The majority of those susceptible were under 2 years of age. In the original study of those without antibodies, 74 per cent responded to Type 1, 58 per cent to Type 2, and 80 per cent to Type 3. Other enteric viruses may have interfered with the response to the poliovirus. In Managua during the 9 months following vaccination there was no case of paralysis; this was an unparalleled experience. About 90 per cent of the children were vaccinated, 272,292 were fed Type 1, 292,188, Type 2, and a similar number, Type 3. In this study about 27,685 were triple negative. Based on the serologic results in 1,141 persons the response was 87 per cent to Type 1, 68 per cent to Type 2, and 87 per cent to Type 3. The disadvantage of this study lies in the previous degree of exposure of the population and the greater likelihood in this area of interference from other viruses.

Doctors F. O. MacCallum, G. Hodges, and M. S. Israel described studies on sudden death in infancy which many have considered as of probable viral origin. No evidence was found to confirm such a supposition, either in earlier studies on fertile eggs and HeLa cells on more than 50 cases or recently, despite attempts with tissue cultures of tissues of babies themselves, HeLa, monkey kidney, or amnion cells and HeLa and infants' tissues treated with x-rays. Suckling mice were also inoculated. Feces, blood, spleen, and respiratory passages were the sources of material studied. In all, 17 cases were studied in detail. A tracheobronchial lesion, similar to that found in more than half the babies, has been produced by Coombs and his colleagues in guinea pigs sensitized by dropping cows' milk into the respiratory tract and subsequently "shocked" by a similar procedure.

Doctors C. H. Chany, M. Cotlenko, A. Nodot, J. Vialette, and M. Lelong of Paris described a mild respiratory illness without fever in infants, many of whom were less than 1 year of age. There were 109 cases and 97 controls. Para-influenza virus 3 (HA1) was found to be the etiologic agent; it was confirmed by Channock.

Doctors S. Kibrick, K. Benirschke, C. Martin, and J. M. Craig added a group of cases to those already reported of Coxsackie B virus disease among the newborn, thus making a total of 47 such cases. From newborn infants with such infections Coxsackie B2, B3, B4, or B5 have been obtained from the feces, myocardium, brain, liver, and other organs. The onset was usually sudden, with fever, listlessness, and feeding difficulty, and with pharyngitis as an early sign. Additional features included evidences of cardiac involvement and failure. Signs were present in the central nervous system in less than one-third, but three-quarters of those examined after death had CNS disease. Of 32 such infants, 7 died within 1 day and 22 within 1 week of onset of illness. Twenty-two of the 47 were infected during nursery outbreaks and the remainder, representing sporadic cases, were usually infected by the mother. Several acquired the disease in utero. Of 28 examined at postmortem, myocarditis was present in all, 76 per cent had meningoencephalitis, 41 per cent had hepatic necrosis or hepatitis, 41 per cent had pancreatitis, and 16 per cent had adrenal cortical necrosis or infiltration. Pneumonitis, local pulmonary hemorrhages, and pulmonary congestion were common.

Dr. P. Tolentino of Genoa reported on the great value of transaminase in the early diagnosis of viral hepatitis.

Doctors T. H. Weller, J. R. Hanshaw, and D. E. Scott of Boston outlined their studies on cytomegalic inclusion disease (CID) which may result from a virus that passes from mother to infant via the placenta. The human fibroblast has been used for tissue culture, but the virus is difficult to cultivate. It is not clear whether the cytomegalic in-

clusion and salivary gland viruses are a single virus or representatives of a closely related group of viruses. Antigenic differences are present favoring the second hypothesis but may be due to long tissue cultivation. Rowe showed that 80 per cent of adults have CF antibodies to a related virus. Neutralizing antibodies were present for a cytomegalic strain in gamma globulin from pools of plasma. Inapparent infection seems to be relatively common. In babies with cytomegalic disease viruria has been known to occur for a 26-month period in 1 case and for a 30-month period in another. It was possible during the neonatal period to cultivate virus from the urine in tissue cultures of human fibroblasts. The positive cultures after prolonged incubation developed focal lesions that often had greenish-brown pigment granules, plus the inclusion bodies. In three groups studied, 27 normal premature infants were negative and 48 infants without CID under 1 year were also negative, while the 9 infants with CID, who from the fourteenth to the one hundred thirtieth day had viruria, averaged 4 pounds 15 ounces in weight. Four of the infants with CID appeared normal at birth but became ill shortly. One developed jaundice at 3 days, 1 at 14 days, and 1 at 7½ weeks. All had splenohepatomegaly, and microcephaly was common. Four had periventricular calcification and 3 had chorioretinitis. At times in such cases intranuclear inclusion bodies are not found in the urine.

Doctors S. Krugman, R. Ward, J. P. Giles, A. M. Jacobs, and O. Bodansky of New York reviewed their extensive studies on viral hepatitis in institutionalized children since 1953. The disease has been endemic, 500 cases having occurred in a population of about 5,000. A group of children were studied in order to note the effect of injections of gamma globulin; they were divided into 2 groups (injected and control) to obtain comparable ages and times of admission in the two groups. The case rates of hepatitis among the 1,771 controls and among the 1,182 injected children for the first year were 22/1000 and 2.5/1000, respectively. Only 3 cases occurred in the injected group at 5, 12, and 50 weeks, respectively, after injection of gamma globulin. In the second year the case rates, in the same order of recording, were 8.9/1000 and 7.1/1000. Four per cent had second attacks. A second experiment demonstrated protection for 5 months after injection and the same incidence of infection in the two groups after 5 months, thus confirming that passive-active immunization had occurred. Serum was found to have virus present during the incubation period and after the beginning of symptoms. In 1 case of inapparent infection, an elevated serum transaminase level was the only definite evidence of infection. The data recorded above are based on jaundiced cases.

Problems of the newborn

Clement A. Smith, M.D.*

BOSTON, MASS.

THE SYMPOSIUM on Current Problems and Progress aimed to provide the congress members who could spare only a little time for problems of the newborn infant with a series of authoritative reviews of controversial questions.

**Associate Professor of Pediatrics at the Boston Lying-in Hospital, Harvard University Medical School; Director of Research on the Newborn, Boston Lying-in Hospital, Boston, Mass.*

Dr. Villee[1] gave a most concise description of metabolism in unborn and newborn life. The essence was that neither fetal nor

neonatal existence normally proceeds under a qualitatively different type of energy metabolism than does adult life, though by a combination of several factors, perhaps not all of them yet understood, the fetus, and probably the newborn infant, can survive longer in an anoxic or hypoxic emergency than can the adult.

Dr. James[2] described the chemical perspective against which we should see neonatal asphyxia. He indicated very strikingly how much clearer a chemical picture emerges when blood is repeatedly obtained from a catheter in the umbilical artery and analyzed for content of carbon dioxide, CO_2 pressure, pH, and buffer base than when only the oxygen content of a specimen of cord blood is analyzed. It appears that not more than the grossest correlation may exist between cord blood oxygen and the chemical status and general condition of the infant at birth. On the other hand, the degree of acidosis and elevation of CO_2 tension may be far more accurate representations not only of the infant's status during the first hour but also of what the infant experienced during delivery. Dr. James has pointed out elsewhere that if one defines some reduction of blood pO_2 plus a rise of pCO_2 and a decrease of pH as a state of asphyxia, all births, even normal ones, involve some asphyxia. We agree with him, but we hope it will not be implied that normal birth is necessarily a bad thing for that reason. What Dr. James did show to be untoward events are difficult, prolonged, anoxic deliveries, births under excessive amounts of anesthesia, and even precipitate deliveries; in each of them the chemical changes of the blood of asphyxia are more marked or more prolonged than after normal births. Dr. James has also shown that, although oxygen administered to the mother before delivery may increase the oxygen level of fetal blood, this association is not necessarily true for blood taken from the cord immediately after delivery.

Finally, Dr. James, like Dr. Villee, suggested that no unusual form of metabolism normally occurs in fetal life, that the fetus has the opportunity of passing excess lactic acid to maternal blood before delivery, and that fetal circulation may have another special resource in the form of extra glycogen found by Dawes in the hearts of fetal animals.

The fact that changes in circulation and respiration at birth can be studied with relative precision and safety by those with special training and proper equipment is worthy of emphasis. This seems one of the two most important features described by Dr. Lind.[3] The other was that circulation during the first few days is a changeable system of pressures and balances which may be altered momentarily in relation to deep respiration or crying by shunts at two levels: the foramen ovale and the ductus. Polleri, Hill, and others showed that this system could be imitated mechanically by complicated electronic mechanisms.

Dr. Karlberg[4] made a highly important distinction between the effects of reduced environmental temperatures on normal premature and term infants (whose oxygen requirements are thereby increased) and on hypoxic, anesthetized, or traumatized infants in whom hypothermia can reduce metabolic rates and may have a function in resuscitation. This observation makes Dr. Silverman's data on the better survival of premature infants in a somewhat warmer environment than of those maintained at lower temperatures seem entirely reasonable, without refuting the reportedly improved survival of anoxic infants who were profoundly cooled by Miller and Westin. Dr. Karlberg's position that distressed infants with rapid respiration might advantageously be cooled until their respiratory rates become normal seems a good compromise.

Dr. Karlberg did not commit himself on the maintenance of normal premature infants in an atmosphere of 15 per cent oxygen except to say that the idea might be reasonable and that the slightly lower body temperatures of such infants in contrast to those kept in room air was physiologically interesting.

Data on effects of high oxygen atmos-

pheres on premature infants are perhaps even more interesting. Karlberg quoted another worker who has shown a repression of cerebral capillary development in experimental newborn animals exposed to extra oxygen for some days and gave some of his own data demonstrating a mild but significant reduction in pulmonary compliance in premature infants exposed to elevated oxygen tension for as little as 4 hours.

Infection was given a relatively and deservedly big place in the first session. The data on immunity, routes of infection, and the clinically applicable methods of blocking these routes and of treating infections when these routes are not blocked rarely have been so well stated. Dr. Wheeler[5] classified the various types of situations that might lead to nursery epidemics on the foundation of immunologic facts outlined by Dr. Vahlquist.[6] If no other part of the transactions of this Congress are to be published, it seems to me that Wheeler's diagrams of circumstances likely or unlikely to cause nursery epidemics should be made available to all.

My main reflection on this matter of infection in the newborn infant is that with available knowledge of the origins of infections before birth, as shown by Dr. Benirschke,[7] and afterward, as shown by Dr. Wheeler, and with current knowledge of immunity and drugs, we should be much further ahead than we are in the prevention of morbidity and mortality from infection. Only 1 other paper was presented on this aspect of neonatal pediatrics. It was from Helsinki and indicated that gamma globulin appeared to be somewhat effective in preventing minor infections but not in preventing major staphylococcal infections in premature infants.

The second session was devoted to physiologic studies of the first and immediately subsequent breaths, to the effects of increased circulation and inflation with air on the mechanical state of the lungs, and to the problem of neonatal resuscitation. Perhaps the most remarkable aspect of the papers was that so much information has been obtained relative to that brief time between emergence of the face at birth and the establishment of breathing. Changes in pulse rate, umbilical artery pressures, and mean blood pressures, before and as breathing begins, were all described, as was the change in the volume of the thorax during the "big squeeze" at birth and the pressure during that squeeze, an event which its measurer did not believe to cause the first breath, although he thought it might facilitate it.

Glossopharyngeal movements, similar to the swallowing respiration or frog breathing, taught to persons with respiratory paralysis were shown to accompany the first breaths of some and perhaps of many infants. Changes associated with respiration have been demonstrated in pulmonary capillaries, which can effect neonatal breathing only as one of several factors. These include the surface tension-reducing factor, which appears to be absent in lungs of small premature infants.

Until we can fit together these data and others not yet available, it is no wonder that we do not try to modify Dr. Apgar's statement that no method of resuscitation is better than direct inflation of the lungs and that it may need to be done earlier than some have been willing to try it, especially in infants with very low Apgar scores. Discussion of resuscitation tended to be about principles rather than about methods. But if the principle arrived at is direct inflation, this will probably require tracheal intubation: a proper procedure for the small number of infants who need it and need it quickly.

One evening a number of us got together to discuss the clinical diagnosis and classification according to severity of "hyaline membrane disease."[8] Neither of these objectives was attained but we decided to recommend a new name, *"idiopathic respiratory distress syndrome of the newborn,"* for the topic of the next morning's conference. That session indeed did contain one reason for the term "idiopathic respiratory distress": the demonstration that mediastinal emphysema capable of causing very severe

distress, not associated with resuscitation, and safely relievable (if necessary) by catheter drainage of air, may occur in approximately 1 of some 700 newborn infants. The remainder of that conference followed a few broad trends: in a rather large statistical study, the etiologic effect of cesarean section by itself in "idiopathic respiratory distress" or "hyaline membrane disease" could neither be proved nor disproved. Cesarean section was shown to increase the risk essentially in premature deliveries where there had been bleeding.

Measurements of circulatory factors should bring us closer to grips with the cardiopulmonary problem of respiratory distress, especially where these measurements are made directly from catheterization of the heart and the major vessels. Nevertheless, only the most cautious conclusions were offered by speakers about such measurements as (1) that the proved shunt through the ductus arteriosus in infants with respiratory distress might be the cause of cardiac failure and resultant pulmonary congestion, (2) that this shunt might provide a mechanical adjustment of the circulation to other primary changes in the lungs, and (3), which was most favored, that patency of the ductus may be part of a general lack of vasopressor tone with increased capillary permeability and hypotension in both circulations. Evidence of systemic hypotension in infants with the clinical syndrome of respiratory distress was abundantly forthcoming from the studies presented. It is interesting that, as reported, blood pressures have not been shown to be significantly reduced in the first 15 minutes after birth in infants who subsequently developed, or are already developing, the respiratory distress syndrome.

Could the underlying cause of the hypotension be a stress reaction to asphyxial disturbances? A good deal of chemical and some endocrinologic data pointing in that direction were presented; these included low serum pH and serum protein, with a high content of albumin in the edema fluid; these changes with new and old data on high serum potassium levels and large urinary excretion of nitrogen, sodium, and chloride suggest an abnormal metabolism of the cells and an increased permeability of the capillaries, such as an asphyxial stress might conceivably produce, although not in one of the "newborn" panels, the discussion of infants of diabetic mothers was interesting in this regard. Dr. Jorgen Pedersen produced evidence that the infants of diabetic mothers, who appear to be so edematous, are actually not waterlogged at birth, but the fat content of their bodies is increased. During the first day or 2 after birth, they undergo a process of increased cellular breakdown with a shift of the cell fluid into the extracellular space which seems to be the basis of the clinically evident edema. This explanation fits in rather interestingly with the possibility of edema from cellular breakdown and increased capillary permeability, not present at birth, in infants with the respiratory distress syndrome, who are not born of diabetic mothers. The purport of all these observations (into which I wish I could fit the demonstrated peculiarities of surface tension of the lungs) certainly justifies further careful attempts at treatment with intravenously administered glucose with or without insulin and sodium chloride or bicarbonate, but I would advise waiting for published details before this treatment is embarked upon blindly or carelessly.

Postmaturity as an obstetrical problem was helpfully distinguished from the placental dysfunction syndrome and from the infant with clinical dysmaturity as pediatric problems; the advantages of classifying dysmature infants clinically into one of 3 degrees or stages were strongly emphasized.

A series of short but interesting reports included: (1) evidence that the oxygen-carrying capacity of the hemoglobin was related to the percentage of the fetal type present; (2) evidence that the oxygen tension of blood coming from the neonatal brain was relatively reduced; (3) analysis of the phases of the cardiac cycle which showed that a short "ejection phase" and a long "tension time" in the newborn do not have the connotation of cardiac failure

which they would in older infants, and (4) evidence that vasomotor control mechanisms undergo qualitative changes or are quantitatively increased (though not first acquired) at 1 to 2 days after birth.

It is apparent that *prematurity* must have different definitions, if it is to be based on physical measurements in different parts of the world; this was shown by the data from Ceylon.

The demonstration of Räihä and others, and presented by Dr. Lind, that the relatively high incidence of prematurity in women with x-ray evidence of small heart volumes can be lowered by reducing their work load seems the most hopeful preventative possibility now in sight. The need for prevention was proved by the 2 accounts of the long-term effects of prematurity: a moderate reduction of stature and a much more serious reduction of coordination, sensory-motor perception, and other needs for normal learning observed in the performance at 10 to 12 years of age by prematurely born children who were considered by their parents to be perfectly normal through childhood.

In selecting among the other aspects of prematurity covered by several speakers, I hope I may be pardoned for concentrating on the one that interested me the most. This was a renewal of hostilities along that stirring old battlefront of how premature infants should be fed. Two developments struck me especially: (1) that there is an increase of total body water and of extracellular water, as measured by dilution techniques, in infants fed for the first 28 days on foods of high ash content (this had been suspected from their appearance but never known before), and (2) that most premature infants can be fed *ad libitum* by nipple, a relatively low solute food at twice the caloric concentration used in our nursery, and beginning as early as 9 to 15 hours after birth, and that they cannot only remain apparently nonedematous but accumulate solid weight at a far greater rate than ours conventionally do. May we sometime have data on a series of 10 times the number presented before others embark on what might be an unsubstantiated observation?

In closing, perhaps the most impressive thing about the whole neonatal section of the Congress is the remarkable and hopeful growth of good clinical, chemical, and physiologic investigations of problems which were regarded as nearly unapproachable not so many years ago. This development cannot fail to be productive of solidly based preventive and therapeutic neonatal pediatrics.

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Nutrition

L. Emmett Holt, Jr., M.D.*

NEW YORK, N. Y.

THE CONTRIBUTIONS to the congress concerned with nutrition may be grouped in three general categories—undernutrition, overnutrition, and special nutritional problems.

UNDERNUTRITION

The major topic in the area of undernutrition was that of kwashiorkor to which two full sessions were devoted. The first session, conducted by Dr. Cicely Williams, dealt with the clinical, pathologic, and biochemical aspects of kwashiorkor, which could be defined as protein deficiency coupled with a variable degree of caloric undernutrition. Some clinical features were pointed out which served to distinguish kwashiorkor from pure caloric undernutrition. In the latter condition the plasma protein level was maintained and the liver was not fatty.

Although kwashiorkor is often designated as a multiple deficiency syndrome, and there is no doubt that it may be associated with evidences of vitamin deficiency, it was pointed out that lesions regarded as specific for vitamin deficiencies could often be cured by the administration of protein or amino acids alone. This had been observed with cheilosis and xerophthalmia. It would seem that the protein component rather than the prosthetic group of an enzyme might be the limiting factor. Dr. Waterlow from Jamaica called attention to the very low nitrogen content of the liver and to the somewhat irregular loss of activity of various hepatic enzymes. Deficiency of *enzyme systems* was stressed rather than deficiency of *particular enzymes*, the most important function of oxidative phosphorylation being preserved at the expense of less vital ones.

Independent observations by Dr. Collis in Nigeria and Dr. Chaudhuri in Calcutta showed that the keto acids, pyruvic and alpha-ketoglutaric, were excreted in excessive amounts and that the administration of methionine would correct this loss. Dr. Metcoff reported abnormalities of the excretion of a number of Krebs cycle intermediates as well as the peculiarities of the electrolyte metabolism in cases studied in Mexico. Dr. Frontali described abnormalities of the amino acid pattern in the urine and Dr. Snyderman reported variations in the pattern of free amino acids in the plasma which differed to some extent in different countries.

Another panel session dealt with the prevention of kwashiorkor and the roles of nutrition, agriculture, economics, and education. The situation varied in different countries. Dr. Williams pointed out that it was only when pediatricians entered a country that kwashiorkor was discovered and recognized as such. The difficult task which belongs to the educator, is how to overcome feeding prejudices and taboos and how

*Professor of Pediatrics, New York University.

to change agricultural practices. Morley pointed out that the best teacher of the mother was someone who cured a patient—a doctor or nurse. Agricultural practices were more difficult to change and commercial introduction of a new food was a very desirable aim. Dr. Achar pointed out some of the economic difficulties. In India popularization of a cheap and useful vegetable food, Bengal gram, had pushed its price up 25 per cent. Dr. Sebrell described the broad approach of the agencies of the United Nations in improving the protein intake of underdeveloped countries. Dr. Senecal stressed the 5 contributing factors—poverty, lack of protein, ignorance, parasites, and infections, and Dr. Scrimshaw reviewed the devastating role of infections. In practical therapy the need for a balanced diet rather than for protein alone was stressed. Dr. Aristia called attention to the desirability and usefulness of fat.

Several papers dealt with the condition of infantile cirrhosis of the liver (Sen's syndrome) as observed in India. The etiology of this condition was not clear. Diet may play a part, but the striking familial incidence suggests a hereditary constitutional factor. Dr. Amala Chaudhuri called attention to the aminoaciduria found in this condition.

A noteworthy contribution to the subject of undernutrition was the report of Hansen on essential fatty acid deficiency in infants fed on fat-free diets. The symptoms observed were looseness of the bowels, excoriation of the anus, and a diffuse, scaly, and exudative dermatitis. The inclusion of a small amount of linoleic acid was curative.

Calcagno and Rubin discussed the value of parenterally administered nitrogen in states of caloric undernutrition when parenteral therapy was necessary. Under these circumstances amino acids given were not all used for calories; some nitrogen was retained.

Several papers dealt with the metabolism of vitamins; Millar described observations made with labelled vitamin K. Gerloczy presented some evidence pointing to the value of vitamin E in the treatment of Leiner's disease and of scleredema of the newborn. Luhby described a functional test for folic acid deficiency based on the excretion of formiminoglutamic acid in the urine.

Abt studied the role of vitamin C in the healing of wounds and established the importance of ascorbic acid in this function. An exceedingly interesting phenomenon was the persistence of ascorbic acid in the scar tissue at the site of a wound for a period of many years.

Weclawowitz described a new and simple test for the evaluation of C deficiency. A drop of 2-6 dichloro-phenolindophenol was placed on the tongue and the time it took to disappear measured.

Raiha reported on the mechanisms concerned in the transfer of vitamin C across the placenta. The need for more vitamin C in the fetus was probably related to the low oxygen tension.

OVERNUTRITION

Forbes introduced the symposium on overnutrition with some statistics showing the untoward effects of overnutrition on longevity and of present pressures tending to make us eat more and more. Mayer discussed the different types of obesity, their physiologic bases, and the endogenous and exogenous factors responsible for them. He felt that the chief fault in our present social structure was the lack of exercise. He pointed out that obese school children were often excused from taking exercise in school. Because of their obesity they were less mobile; thus a vicious cycle developed. He called attention to the fallacy that exercise invariably increased appetite and consumption of food. His experimental studies indicated a possible therapeutic role of glucagon.

Prugh discussed the psychogenic factors leading to obesity, as, for example, neglected or ill-adapted children who turned to food for solace and mothers who compensated for their own parental inadequacy by pushing food into their children. The difficulties of psychotherapy were stressed and

the fact that in certain instances strenuous efforts to overcome obesity might be harmful. It was a life-time problem in many instances, whereas in others corrective factors became operative at puberty.

Hegsted spoke briefly but pointedly on the effects of overnutrition with minerals. He mentioned certain conditions caused by excesses of certain elements in natural foods such as fluorosis. The Kashin-Beck syndrome occurring around Lake Baikal due to an excess of iron was also mentioned. He pointed out that overenthusiasm for one mineral might affect adversely the retention of another. Animal studies showed that an excess of molybdenum might lead to copper deficiency and an excess of calcium to zinc deficiency. He called attention to the unduly high calcium requirements proposed by various authoritative bodies, requirements which would indicate that breast milk did not provide enough calcium. Hegsted felt that nature had done a pretty good job with breast milk and also called attention to the lack of a syndrome of hypocalcemia and mentioned the milk-alkali syndrome. This paper was discussed by Harrison. Both he and Hegsted stated that they agreed with each other perfectly, but to an observer there seemed to be a slight difference in their point of view. Harrison felt that the Creator really would have liked to have put more calcium in breast milk but that he refrained from doing so to avoid depleting the mother and compromised by putting only the bare minimum calcium needed by the child into the milk. One wonders why the Deity was less tenderhearted when he faced the problem of depleting the mother cow for the sake of her calf.

Hegsted also discussed the question of the margin of safety from undernutrition and pointed out that at least an equal margin of safety against overnutrition should be provided.

Halac discussed the question of protein stores induced by high protein diets and reported experiments in rats in which such stores were challenged by various stresses such as exercise, heat, cold, Metrazol poisoning, x-irradiation and privation of water, food, or protein. In no instance did the animals fed a high-protein diet do better, and in most instances they failed to do as well. Filer reported experiments with growing pigs whose body composition was altered by diet even more than was the case with rats. Here again fat reserves were found to be better than protein reserves for withstanding dietary stresses.

Harper discussed the question of specific amino acid imbalances in diet. It was clear from animal studies that one could improve the quality of protein by supplementation with amino acids. It was also clear that excesses of particular amino acids could unbalance a diet and have undesirable effects. The question of supplementation of human diets with amino acids depended on the demonstration of a need. Replying to a specific question in regard to the need for lysine supplementation, he stated his unawareness of such a need.

Schreier spoke here and in another section of his observations on milk supplementation with lysine in normal and malnourished infants. No consistent improvement of nitrogen retention was observed and some evidence of a general aminoaciduria developed.

Holman described extensive observations on the fat staining of the aorta in autopsies on young children often before the age of 3 years. He felt that this was the first stage of atherosclerosis. Although by no means convinced that atheromatous disease was nutritional in origin, he felt that it was definitely a pediatric problem. The question as to whether fatty streaking really was the initial phase of atheromatosis was debated by Ahrens.

Pomerantze studied blood cholesterol levels in infants fed various levels of unsaturated fat and noted that the use of unsaturated vegetable fats resulted in lower levels of cholesterol. If vegetable fat were added to a whole-milk diet the added calories might lead to overnutrition. Snyderman pointed to the relation between protein nutrition and blood cholesterol levels. Omission of a single amino acid caused a

prompt reduction of the level of blood cholesterol.

SPECIFIC NUTRITIONAL DEFECTS

Talbot gave a most interesting address on the ability of the body to adapt to various untoward situations, both congenital and acquired when its nutrition is maintained within proper limits.

The sessions dealing with metabolic disease brought to light a number of new or relatively new syndromes and added to the knowledge of several of the more familiar disease entities. Among the new metabolic errors described were the following:

Holzel described a hereditary condition in which lactose is not split in the gut, resulting in defective absorption and failure to thrive with a tendency to flatulence.

Prader described a familial condition of hereditary fructose intolerance caused by a defect in the enzyme fructose—1-phosphate aldolase. When fructose or cane sugar is given there is sweating and trembling. The condition is associated with mental defect, and the liver may be affected. The blood sugar and especially the blood phosphorus are markedly lowered by giving fructose.

Moncrieff called attention to the syndrome consisting of the triad, saccharosuria, mental defect, and hiatus hernia, a triad difficult to explain on the basis of a single enzyme defect.

Ahrens described a new type of idiopathic hyperlipemia (or rather triglyceridemia) in which the administration of a high fat diet corrects the error rather than accentuating it.

Menkes discussed the recently discovered syndrome of "maple syrup urine disease," a metabolic error involving the 3 branched chain amino acids, leucine, isoleucine, and valine, as well as methionine. Clinically this declares itself in very early life with neurological lesions leading to rapid cerebral deterioration and death. The urine and sweat have the odor of maple syrup. The exact nature of the metabolic anomaly is not yet clear; therapeutic studies with correction of the amino acid imbalance are in progress.

Lowe described a syndrome resembling in some respects the De Toni-Fanconi syndrome which he designates as oculocerebral dystrophy. Its peculiar features are the association with ocular lesions and an extreme degree of amentia. The hereditary pattern is that of a sex-linked recessive.

Cochrane discussed the type of infantile hypoglycemia which is precipitated by the administration of leucine as such or in the form of protein. The rat appears to be a good experimental animal which shares this metabolic peculiarity.

Childs and Cooke discussed a new metabolic anomaly involving the interconversion of glycine and serine and associated with marked glycinuria. Clinically there was mental retardation, digestive disturbance, neutropenia, and cyclic thrombocytopenia.

Klein reported a group of patients with an unusual type of familial periodic paralysis associated with high serum potassium levels. Bed rest precipitated attacks. There were indications that the uptake of potassium by the muscle was inhibited. Benefit was obtained from glucagon therapy.

A number of new features of more familiar metabolic anomalies were also described at these sessions. De Toni described a new metabolic anomaly, hypercitruria, in the De Toni-Debré-Fanconi syndrome, which, if eponyms are to be discarded, must now be designated as *"gluco-phospho-amino-citro diabetes."* He also described an acquired type of the disease from which recovery is possible.

Bessman described some secondary anomalies of tryptophan metabolism in phenylketonuria, which revealed how readily a single metabolic block may lead to a complex picture of disturbed metabolism.

Physiologic aminoaciduria of the newborn was discussed and some new features described; these included the failure of phenylalanine to participate to any great extent in this (Bickel) and the excretion of methyl glycine at this time (O'Brien).

Armstrong discussed the all important question of the early diagnosis of phenylketonuria and showed that it can be detected by an elevation of the blood phenylalanine, often in the first 2 weeks of life before the urinary change develops. For routine testing of normal infants, testing of the urine for phenylpyruvic acid before the age of 5 weeks or of the diapers with test papers is desirable. In the case of siblings from affected families, testing of the blood during the first 2 or 3 weeks is indicated. He also gave a follow-up on the effects of very early treatment. It seems clear from present data that normal I.Q.'s can be obtained. Whether mental development suffers minimally in some of these infants treated early is not yet clear.

Dorfman reported on the early recognition of Hurler's syndrome by the detection of chondroitin-sulfuric acid in the urine.

Donnell and Hsia discussed the detection of the heterozygote carrier of galactosemia by means of transferase enzyme measurements of the red blood cell. It appeared that the method of Hansen used by Donnell for detecting this enzyme permits the most accurate detection of the carrier state. Data were also presented on the treatment of galactosemic patients begun at different ages, which showed the importance of early treatment in preventing brain damage.

A number of papers dealt with glycogen disease. Several new forms of this malady were described. Van Creveld described a case in which only the muscles were affected.

Hers described 3 different types of enzyme defects in the hepatic form of the disease: (1) a defect of phosphorylase, (2) a defect of glucose-6-phosphatase, and (3) a defect of the branching enzyme.

Cochrane described a specific loading test with dihydroxy acetone for the diagnosis of the disease. There is no rise in blood dihydroxyacetone in von Gierke's disease.

Two new forms of therapy were reported: the use of glucagon by Lowe and of citrate by Sidbury. The latter also reported on the high glycogen content of the red blood cells.

Finally, Van Creveld gave a long-term follow-up report on his original 2 patients studied over 30 years. They are completely normal clinically, but show minor abnormalities in the blood sugar curves after administration of epinephrine.

There were several interesting reports on technical procedures, particularly in the section on chromatography, which time does not permit reviewing. Nor is it possible to review the symposium on infant feeding which is now in session.

An extraordinary degree of progress has been reported in this area of pediatric interest and we are indebted to Dr. Ebbs and his colleagues on the Program Committee for what they have given us.

Surgery

Lawrence K. Pickett, M.D.*

SYRACUSE, N. Y.

IT WAS pleasing to this observer to see how many of the different disciplines of medical pediatrics were of interest to the surgeons and to be aware of how many of the sessions a surgeon should have attended. Since I could only be in one place at one

**Clinical Associate Professor of Surgery, State University of New York, Upstate Medical Center, Chief Pediatric Surgery, Syracuse Memorial Hospital, Syracuse, N. Y.*

time my summary is limited to the sessions I attended.

Dr. Herbert Coe opened the pediatric surgical aspect by his informative discussion of the history of pediatric surgery. As is generally known, humility is not a characteristic indigenous to surgeons. Dr. Coe, however, was most humble in his lack of referral to his part in the development of this specialty and in his encouragement and fostering of many young pediatric surgeons.

Dr. Clatworthy pointed out the relationship of hydramnios to congenital anomalies responsible for high obstruction of the gastrointestinal tract, especially esophageal, duodenal atresia, or some other defect blocking the intestinal tract above the jejunum. No relationship with hydramnios was noted with obstructions below the jejunum in the ileum or the colon. The fetus is estimated to exchange 600 to 2,000 ml. of amniotic fluid per day.

Dr. Fegetter of England and Dr. Benson of Detroit discussed atresias of the small intestine. The possibility was presented that such atresias do not result from an error in the transformation from the solid cord to the tube stage of embryonic development but more likely from a vascular accident to the bowel in prenatal life.

Dr. Swenson gave a follow-up on 200 cases of congenital megacolon, pointing out the difficulties and the increased risk of operation in the first year of life and the necessity for an immediate colostomy rather than trying to tide them over medically. Thus the case fatality rate of the syndrome of pseudomembranous enterocolitis in the untreated infant under a year of age with congenital megacolon has been variously estimated to be 70 to 90 per cent. Early colostomy with deferment of definitive operation until after a year of age has reduced this mortality rate to 14 per cent, and Swenson feels this rate can be lowered still further. He also advised against the use of antibiotics to prepare the bowel for operation, pointing out that such therapy could result in overwhelming sepsis.

Mr. Nixon of England and Dr. Bill of Seattle each summarized Keith's discussion of the embryologic formation of the imperforate anus. Most pertinent, however, was the conclusion that the surgical phase of the care of the infant with an imperforate anus is perhaps the least important part of the therapy. The follow-up care, the education of the parents, and the training of the child in defecation are the most important aspects. The child must be taught to defecate at a scheduled time rather than to depend on the urge, since the neural mechanism for the urge of defecation is destroyed surgically or never was present.

Dr. Carey of Belfast estimated the incidence of a partial thoracic stomach to be equal to that of pyloric stenosis. He bravely concluded before a group of surgeons that the treatment of this disease was totally medical.

Perhaps the most encouraging feature of the surgical sessions was the lack of thumping of chests by the surgeons and the absence of presentations based on 950,000 successful cases of this or that, but rather presentations of research designed to determine the etiology of anomalies and methods for their prevention.

General summary

Charles A. Janeway, M.D.*

BOSTON, MASS.

IN BRINGING the Scientific Program of this memorable Ninth International Paediatric Congress to a close, I wish, first, on behalf of all who have participated either as listeners or as speakers, to express our thanks to our hosts, the Canadian Paediatric Society, to Dr. Ross and his Organizing Committee, to Dr. Ebbs and the Program Committee, and to the literally hundreds of people who have spent most of their time at the Congress making sure that arrangements in all the conference rooms were satisfactory and that the various sessions have run smoothly.

What comments can we make, and what conclusions can we draw from this remarkable program in which we have been privileged to participate? One comment I heard was that this was not just a Congress of Paediatrics, but rather one of pedology. In other words, this Congress has been concerned with the sciences relating to children, as well as with their application to child health. The vast reservoir of knowledge at the basic level, upon which we must found our practice of pediatric surgery or pediatric medicine, has grown enormously, as is perfectly apparent from the broad scope of this program, which, even so, could not be complete in the fullest sense of the word. This has led to specialization within the program, which in turn reflects the essential specialization which has developed within the field of pediatrics. This is an inevitable trend as knowledge grows. Pediatrics is a specialty in only one sense of the word, in its subjects, that is, children. This is a very different kind of specialty from genitourinary surgery or other regional or technical specialties of this type. It is concerned with everything which affects the health of children, so that, as knowledge concerning those factors which affect the physical and mental health of children grows, as diagnostic procedures, surgical techniques, and effective drugs increase in numbers and complexity, specialization becomes increasingly inevitable. It can't be helped; many of us may regret it, but it is here to stay. Certainly none of us would want someone to operate upon our own child who did not know his special field completely. There is a limit to the amount of knowledge which the human brain can retain; the amount which the particular brain in my skull can comprehend at this moment is extremely small and has long since reached the saturation point, and I think we all have to agree that none of us can any longer grasp all pediatric knowledge.

The beneficent effects of specialization have been demonstrated amply by the proceedings. I think of two very clear examples: first, the presentation by Dr. Taussig, which was the culmination of the Sessions

*Thomas Morgan Rotch Professor of Pediatrics, Harvard University Medical School; Physician-in-Chief, Children's Hospital Medical Center, Boston, Mass.

on Congenital Heart Disease, in which some of our members spent almost their entire time at the Congress. The specialties of pediatric cardiology and cardiac surgery have their justification in the children who are now walking around relieved of disabilities which a few years ago were considered hopeless. Second, Dr. Farber's discussion of the attack upon cancer in childhood, a disease so complicated that it cannot be diagnosed and treated in its entirety by any one man, but requires the collaboration of pathologists, pediatricians, surgeons, radiologists, biochemists, and pharmacologists, all of whom must work in concert, not only in research upon this disease, but in making sure that the affected child receives the optimal care which modern science can now provide, care which was almost unthinkable when these Congresses first began, or even 2 or 3 Congresses ago. Our task as pediatricians is to translate the scientific work which is going on at all the frontiers of the biologic sciences as rapidly as possible into more effective prevention and treatment of disease and the promotion of better health for children in the total sense of these words.

I should like to compliment the Program Committee for having the courage to open the Congress with the Symposium on the Cell. This was a relatively unique experiment in providing a firm foundation of basic science for a clinical meeting, particularly appropriate for this one, since pediatricians are concerned with everything that happens from man's start as a unicellular organism until he achieves his full stature and physical maturity. It gave us all a valuable glimpse into the future of biology and into areas of biologic science which certainly will have an enormous impact upon our daily work as pediatricians in the future and which will undoubtedly mold the program of many Congresses to come. First, one of America's foremost biologists, Dr. Paul Weiss, discussed the problems of cellular differentiation and admitted that nobody knows what makes a cell of a certain type behave as it does, although it exhibits this propensity very early in its life. He spoke about the growth and development of the cell, a process which goes on from the time it is first produced by cell division until the total organism dies. Next we heard from Dr. Bonner about the growing body of knowledge of the genetic control of cellular biochemistry, and therefore of the manifestations we see as clinicians, through patterning the synthesis of those all-important proteins, the enzymes, which mediate and catalyze the biochemical reactions which make us what we are. Then from Dr. Davis, a microbiologist who has also been a professor of pharmacology, we learned how the cell is controlled by and adapts to its environment through mechanisms whereby the end products of enzyme reactions may shut off the formation of enzymes that are not needed. These are the chemical bases of those processes of adaptation which we observe as child behavior. As yet we can't make many connections between behavior and specific biochemical phenomena, but these connections will ultimately be recognized, just as certainly as we are sitting here in this room. To have Dr. Lehninger show how the beautifully organized phenomena in the mitochondria, which are the engines of the cell, provide the basic energy that makes other synthetic processes possible, and to hear Dr. White, as an anatomist and biochemist, discuss the interaction of enzymes and hormones and how the hormones regulate bodily processes through their control of the rates of enzyme synthesis and therefore of the rates of the biochemical reactions which they mediate—this has been a rare privilege for all of us. The basic knowledge which has been presented has permeated and illuminated much of the discussion that has gone on in the program since that first day.

I would like to stress a few points very briefly. First, these sessions have illustrated the extent to which advances in scientific medicine have been dependent upon advances in technique. These advances in technique in turn have been created by imaginative people. The Virology Sessions would not have occurred without the deve-

opment of the techniques of tissue culture and electronmicroscopy; much of what we heard about metabolic disease was dependent upon advances in enzymology made by the biochemist and upon the knowledge of proteins which has come from better techniques for their study, many of them quite simple and applicable to clinical problems. Finally the beautiful piece of imaginative work which produced a method for counting the actual number of chromosomes in the human cell has brought us up against the age-old biologic problem of heredity versus environment. Are the chromosomal abnormalities hereditary or may they be induced by changes in the environment at a very early stage? This dilemma was illustrated in the discussions on Mongolism, in which people still cannot agree upon which of these factors is primary.

Second, the title of Dr. Holman's paper, "Atherosclerosis: a Pediatric Nutritional Problem?," emphasizes the necessity for long-term critical study of our pet pediatric ideas. The validity of our current nutritional recommendations or child-rearing practices cannot be judged solely by the rate of weight gain or by the apparent emotional adjustment in infancy but must be tested in terms of morbidity and mortality in adult life. So we cannot afford to separate ourselves completely from adult medicine, for the end results of our attempts to bring up healthy children will be judged by our internist colleagues. If we overemphasize one aspect of health it is quite possible that we may be laying the foundation for degenerative disease in later life.

There is much to say and no time to say it. At the end of this Congress the pediatrician feels somewhat schizophrenic, pulled in one direction by his interest in the whole child and driven in the other by the necessity for dividing the child up into small pieces in order to study him. As a clinician he must try to put all these pieces together in the care of a specific child; as an investigator he must probe deeply into one small area. And finally, as a world citizen, he is torn between his intense devotion to scrutinizing the last details of biochemical processes, a procedure which has led to such striking scientific advances, and his chagrin at the failure to put into practice so much of what he now knows; he is distressed that social, economic, and cultural barriers still stand in the way of giving so many children, perhaps the majority of children in the world today, the benefits of scientific pediatrics.

This has been a memorable week; the community of interest, the unity of purpose, and the comradeship we have enjoyed, as well as the opportunity to exchange a wide variety of ideas and experiences, have probably been even more important than any of the formal scientific sessions, but these had to be organized to make these less tangible benefits possible. So, in closing the scientific program, let me express my own sense of humility and gratitude for having been here and the hope that we may all meet together again 3 years from now in Lisbon.

CLINICAL PATHOLOGICAL CONFERENCE

THE CHILDREN'S MEDICAL CENTER, BOSTON, MASS.

Sidney Farber, M.D., Editor
Gordon F. Vawter, M.D., Assistant Editor

THIS 14½-year-old girl was readmitted to The Children's Medical Center with the complaint of chest pain which had begun 6 hours before admission.

The mother and the mother's brother have been studied for anemia. The mother is of Italian parentage and the father of Greek origin. The patient has 1 sibling who is well.

This is the sixtieth admission to The Children's Medical Center of this child, whose natal history is unremarkable but who was treated with iron, liver, vitamins, and transfusions, after anemia was proved at 3 months of age. She was first admitted at 11 months of age with pallor, history of irregular gain of weight, hepatosplenomegaly, cranial bossing, and low-grade fever. The blood contained hemoglobin, 6.6 Gm. per cent; leukocytes, 34,600 per millimeter^3 with 51 per cent polymorphonuclear leukocytes, 43 per cent lymphocytes, 22 nucleated red blood cells per 100 leukocytes, and adequate platelets. The blood smear showed hypochromia, constant microcytosis (later, macrocytes were often described), and marked anisocytosis and poikilocytosis. Reticulocytes were 6.6 per cent. Sickling was not found. The span of saline fragility of erythrocytes was only slightly increased. Serum bilirubin was 0.5 mg. per cent direct and 2.1 mg. per cent total.

She was admitted every 4 to 6 weeks for 1 to 3 transfusions over the next years until the present time. Her skin color darkened, and firm hepatosplenomegaly increased. It became increasingly difficult to find completely compatible blood and transfusions of washed and packed erythrocytes in saline were covered by antihistaminics and aspirin. During this period a positive direct Coombs' test was recorded. For the past 7 years tachycardia, cardiomegaly, episodic apical diastolic murmurs (in addition to her regular apical Grade 2 systolic murmur), and transient gallop rhythms were benefited by transfusion. Ecchymoses, bleeding gums, epistaxis, and bloody diarrhea had each been noted once or twice. At age 10$^8/_{12}$ years, the enlarged spleen was removed and the white blood cell count rose from 3,500 to 8,000. The gall bladder appeared normal at that time. A fasting blood sugar was 144 mg. per cent, but urinalyses were negative for sugar and acetone until more recently. When she was 12$^9/_{12}$ years of age there was spontaneous subsidence of a 2 weeks' illness beginning with nausea, vomiting, fever (102° F.), and a tender liver. There were 4 plus bilirubin, hemoglobin, 5.4 Gm. per cent, leukocytes, 33,000 millimeter^3 with 43 per cent polymorphonuclear leukocytes, 36 per cent lymphocytes, 10 per cent atypical lympho-

cytes, 11 per cent monocytes, and 85 nucleated erythrocytes per 100 leukocytes, negative heterophile agglutination, and bilirubin 7.7 mg. per cent direct and 11.7 mg. per cent total. Thymol turbidity and cephalin flocculation were both 3 plus.

PRESENT ILLNESS

At 12 10/12 years of age there was sudden substernal pain which was worse on respiration, without objective findings. Hemoglobin was 7.5 Gm. per cent. The discomfort responded in 5 minutes to codeine. A respiratory infection preceded this attack by 1 week, and palatal vesicles were noted during the acute episode. Over the next 1½ years there were 6 to 7 episodes of chest pain (usually precordial), often occurring after transfusion and often associated with temporary changes in S-T and T waves electrocardiographically, but without changes diagnostic of infarction. Eight weeks before this admission she was placed on digitalis maintenance. She was hospitalized for 4 weeks beginning 2 weeks later for recurrent pain which was worse on inspiration and on lying down. Cardiac dullness was increased, heart sounds were muffled, and a precordial friction rub heard initially disappeared but recurred 4 days later; a transient pulsus paradoxus was noted but the lungs were clear. Vital signs were pulse, 100 per minute, respirations, 36 per minute, and blood pressure, 110/70 mm./Hg. Fluoroscopy showed the cardiac shadow to be enlarged in all directions, with almost no visible pulsation. EKG showed low voltage. She was transfused carefully and improved dramatically after 5 days of therapy with cortisone (300 mg. per day, which was tapered to 100 mg. per day). She re-entered the hospital 5 days after discharge because of precordial pain.

Physical examination revealed a low-grade fever (temperature of 101.8° F.); other vital signs were essentially as before. She weighed 77 pounds and was small, thin, chronically ill, darkly pigmented, and in acute distress. The heart was enlarged to the midaxillary line. Heart sounds were good in quality, with the usual murmurs. Neck veins were distended and pulsatile. The liver was, as usual, palpable 13 cm. below the costal margin and had an irregular surface. Pedal edema was mild.

Urinalysis gave normal findings, apart from a single plus reducing substance. The blood contained hemoglobin, 7.9 mg. per cent, 44,300 leukocytes per millimeter^3 with 90 per cent polymorphonuclear leukocytes, 9 per cent lymphocytes, 1 per cent monocytes, and 22 nucleated erythroid forms per 100 leukocytes. Blood smear was unchanged. Nonprotein nitrogen of blood was 32 mg. per cent. The albumin-globulin ratio of plasma was 3.5/4.7 Gm. per cent.

She responded to anticongestive measures with transient appearance of a precordial friction rub. On the tenth hospital day a thoracotomy was performed.

DR. M. BALDINI.* This 14½-year-old girl has been ill all her life. The disease, which was already apparent at 3 months of age and which, most probably, represents the background against which all the rest of the pathologic history developed, is a chronic, congenital anemia. It is probably hereditary, since it is reported that the mother and her brother had been studied for anemia. At 11 months of age, when the first of her 60 hospital admissions occurred, the anemia already presented sufficient characteristics for its definition. The reticulocytes were elevated, the indirect serum bilirubin was increased, and there was hepatosplenomegaly. The anemia seems, therefore, to be hemolytic in type. The cranial bossing, which was also present at this time, is suggestive of high degree of hypertrophy of the bone marrow in early life and would indicate a severe hemolytic component in this anemia. It would be of interest to demonstrate the x-ray films of the skull at this point.

DR. E. B. D. NEUHAUSER. These films were made when the patient was about 7

*Dr. Baldini is Associate Professor of Medicine, Tufts University School of Medicine, and Associate Director, Blood Research Laboratory, New England Center Hospital.

years old and I imagine that there have been changes for the worse. There is a characteristic thickening of the diploe with a tendency toward vertical striations. The bones of the base have increased density with striking changes about the facial bones and maxillary sinuses. There were no films of the skull after this date.

DR. M. BALDINI. It is clear then that bossing of frontal and parietal bones of the skull in this child was not associated with thickening of the bony plates as in rachitic hyperostosis. On the contrary, there was widening of the diploic space and suggestion of radial pattern of the diploic bone. Pneumatosis of the maxillary sinuses was also present. These changes are most often seen in patients with Mediterranean anemia, but they are not specific for this disease and can be found in any congenital hemolytic anemia. The fact that they were present in this patient as early as 11 months after birth indicates that the blood disorder had manifested itself in the newborn period when the bony cortices offer less resistance to the growing tissue of bone marrow. Caffey[1] found these changes as early as 4½ months of age in children with congenital hemolytic anemia.

The examination of the peripheral blood brings further data for the differential diagnosis of this anemia. The white blood cells were 34,600 per millimeter[3] with normal differential. This may confirm indirectly the hemolytic type of anemia, since it is known that in the presence of increased hemolysis the leukocyte count is often increased, especially in children. This, however, rarely exceeds the figure of 20,000 to 25,000 per millimeter,[3] and I wonder whether the figure of 34,600 includes the nucleated red blood cells since erythroblastemia was present here.

DR. L. K. DIAMOND. The values reported are uncorrected.

DR. M. BALDINI. What is of basic importance in the differential diagnosis of this congenital, hemolytic anemia is the hypochromia and microcytosis of the red cells. This hypochromia was not related to iron deficiency because no response to iron treatment had been obtained. The hypochromia here was rather the manifestation of an intrinsic defect of the red cells, which points to the diagnosis of thalassemia or to a combination of some other constitutional hemolytic anemia with the thalassemia gene. Other congenital hemolytic anemias are typically normochromic. This holds for hereditary spherocytosis, hereditary nonspherocytic hemolytic anemia, and also for sickle cell anemia and other hemoglobinopathies. The hypochromia of the red cells in thalassemia is the manifestation of a defect in the synthesis of heme which is typical of this disease. Grinstein and colleagues[2] have demonstrated that in vitro the uptake of iron[59] into heme by blood from Cooley's anemia patients is lower than normal. This appears to be due to a partial block in the incorporation of iron into protoporphyrin for the synthesis of heme.[3]

Variable numbers of target cells are usually found in the peripheral blood of patients with thalassemia and I would like to know if they were found in our case.

DR. L. K. DIAMOND. Target cells were almost always present, although not a large number of them.

DR. M. BALDINI. This agrees with the observation that the span of the osmotic fragility of erythrocytes was only slightly abnormal. If I understand correctly, this was found to be increased on both ends of the curve, indicating the presence of both a certain number of cells with decreased osmotic fragility and of others which were abnormally fragile. This double type of red cell population is not an uncommon finding in cases of thalassemia in which hemolysis is severe, although the majority of the cells usually show increased resistance to hypotonic saline. The fact that the number of target cells and the degree of osmotic resistance of the red cells were not striking in this patient is in accord with the variability of the hematologic abnormalities in patients with thalassemia. These abnormalities often do not correlate even with each other. For example, it is

known that rate of hemolysis and amount of fetal-hemoglobin are often not in direct relationship. The same can be said for number of target cells and degree of osmotic resistance or rate of hemolysis.

Hematologic and clinical characteristics in this patient, the family history of anemia present in the mother and her sibling, the Mediterranean ancestry, the congenital hemolytic disease associated with bone deformities, the severe hypochromic, microcytic anemia resistant to iron treatment, the erythroblastemia, the hepato- and splenomegaly, and also the frequent low-grade fever all point to the diagnosis of thalassemia major. It is improbable that the patient had one of the variants of thalassemia, that is a combination of a single thalassemia gene with another gene responsible for the production of an abnormal hemoglobin. Sickle cell thalassemia can be discarded because the sickling phenomenon of the red cells was absent. Hemoglobin C-thalassemia and hemoglobin E-thalassemia only manifest themselves with mild anemia and a less malignant course of disease. Less common "intermediate" types of constitutional hemolytic anemia have been described,[4, 5] however, and the possibility in our case of a hemolytic, hypochromic anemia developing as a consequence of the admixture of two distinct traits for congenital anemia can only be ruled out by more special studies, mainly hemoglobin electrophoresis and starch-block electrophoresis.

DR. PARK S. GERALD. Unfortunately, the patient needed transfusion so often that this prevented accurate studies of the hemoglobin. The blood of both parents contained an abnormally increased amount of hemoglobin A_2, whereas that of the sibling was normal. These findings fit well with classical thalassemia.

DR. M. BALDINI. Although thalassemia major, i.e., Cooley's anemia, is always progressive and fatal, the course of the patients varies greatly. From several clinical studies in Italy[6] it seems that the prognosis of a patient with Cooley's anemia bears a relationship to the time of life in which the symptoms of the disease first appear. Cases in which the anemia and hepatosplenomegaly are apparent before the third month of life usually have the more severe and rapid course with death in infancy, while patients in which the disease appears in the second semester may reach puberty. On rare occasions the disease manifests itself only after the second year of life. These are usually the rare patients who may reach adulthood.

All of the rest of this patient's large history can be considered, in some respects, as a number of complications occurring against the background of thalassemia.

The requirement for blood transfusions increased progressively and soon 2 to 3 transfusions every 4 to 6 weeks had to be given. As often happens with patients receiving large numbers of blood transfusions, it became increasingly difficult to find completely compatible blood. The patient probably became sensitized to some blood factor(s) that she lacked. During this period of time a positive *direct* Coombs' test was observed. This is a very unusual finding because, as a rule, multiple transfusions may cause the development of antibody against any blood factor which is not present on the patient's cells. But this antibody would react against the donor's cells and not against the cells of the recipient, and thus it would result in a positive indirect Coombs' test. There is the possibility of an "iatrogenic positive Coombs' test" as mentioned by Kevy and Morrison.[7] On rare occasions a patient may be given a transfusion with blood possessing antigens for which his serum possessed the corresponding antibody induced by previous transfusions and which had been missed by the cross match technique used. If there are many sensitized transfused red cells in comparison with the patient's own red cells and they are tested before they are destroyed, a transitory positive direct Coombs' test may be found. But these are only rare occurrences which I have never seen myself. Ordinarily, a direct Coombs' test can be found in isoimmune (Rh) disease, in autoimmune disease, and

occasionally in lead poisoning.[8] Heavy metals coating the red cells may produce changes on their surface capable of inducing agglutination in the presence of an antiglobulin serum.[9] The temporary phenomenon of a positive direct Coombs' test in our patient may be considered as a self-limited, intercurrent episode, the nature of which remains unexplained. Perhaps Dr. Diamond may like to express his opinion on this problem.

DR. L. K. DIAMOND. We could not explain it either. On only one occasion 3 years ago was a 2 to 3 plus Coombs' test found by a direct test on the patient's own cells and confirmed by the Blood Grouping Laboratory. At no time was it possible to demonstrate any isoantibody in the patient's serum against any donor's cells. Therefore she has no obvious antibody against any of the blood she has received, and at no time since have we found a positive Coombs' test.

DR. M. BALDINI. The large requirement for blood transfusions in our patient cannot be explained only by a reduced response of the bone marrow to the anemia. More likely, the splenomegaly acted as an extracorpuscular factor producing additional destruction of the patient's own erythrocytes and also reducing the life span of the donated red cells. The hemolytic effect of splenomegaly in Cooley's anemia has been documented well by Lichtman and associates.[10] In our experience "hypersplenism" with all its consequences is not uncommon in patients with thalassemia with massive splenomegaly. With "hypersplenism" single or multiple cytopenias develop and disappear only after splenectomy. This is most probably why in our patient the white cell count which had decreased to 3,500 went to 8,000 when the huge spleen was removed 4 years ago. This may also explain why the few hemorrhagic episodes which the child had had from time to time and which probably were due to thrombocytopenia did not repeat themselves after splenectomy.

One of the dangers of multiple transfusions in any chronic type of anemia not due to loss of blood is the development of hemosiderosis and consequent tissue damage. During her life our patient received an average of about 24 transfusions per year which would amount in 10 years to the introduction of approximately 60 Gm. of iron. There is no precise knowledge of the number of grams of iron and other factors necessary to transform transfusional hemosiderosis into exogenous hemochromatosis with parenchymal damage and fibrosis mainly of the liver, pancreas, and myocardium, but it is known that this may occur in patients who have been "over-transfused."[11-13] The hyperglycemia and, later, the glycosuria in our patient would suggest that hemochromatosis developed in the more recent years. Darkening of the skin and, in part, the hepatomegaly and the chronic heart failure also could be attributed to the damage of excessive storage of iron.

At the age of 12 the patient had a 2-week episode of nausea, vomiting, fever, and a tender liver associated with increased direct bilirubin and bilirubinuria, most probably attributable to infectious hepatitis.

In the last 2 years the patient's heart condition has come to the foreground. Cardiomegaly had been already recorded 7 years ago along with tachycardia, systolic and episodic diastolic murmurs, and transient gallop rhythm. Since the latter symptoms were benefited by transfusions, they were probably functional in origin and caused by the anemia. But the cardiomegaly certainly had a more profound organic cause, since, in chronic anemia, fatty degeneration of the myocardium occurs and it is usually found in protracted cases of Cooley's anemia. Furthermore, in this patient, myocardial hemochromatosis may have also had its role. Heavy deposition of iron in the myocardium usually causes edema, fragmentation of muscle fibers, focal necrosis, fibrosis, and fatty infiltration with consequent cardiac arrhythmia and even congestive heart failure.

Superimposed on the patient's chronic heart condition, several acute episodes, mainly characterized by precordial pain,

appeared more recently. The first of these episodes occurred 2 years ago after a viral type of respiratory infection. The substernal pain was worse on respiration but there were no objective findings. Other episodes of precordial pain recurred, particularly after transfusions. More specific was the recurrent precordial pain that brought the patient to the hospital 6 weeks ago. At this time cardiac dullness was found increased, heart sounds were muffled, a precordial friction rub was heard, and a transient pulsus paradoxus was noted. These were typical signs of pericarditis with effusion. This diagnosis was confirmed at fluoroscopy. The episode improved dramatically with cortisone, but recurred 5 days after discharge from the hospital. During the present admission a transient precordial friction rub again was heard.

To give an etiologic definition of an acute, recurrent pericarditis is often difficult. The considerable number of attacks in this patient would probably exclude myocardial infarction. Furthermore, electrocardiographic changes were not in favor of this diagnosis. The absence of signs of rheumatic fever and the spontaneous regression of the attacks would make the diagnosis of rheumatic, tuberculous, or septic pericarditis less probable. Hemosiderosis per se is not known to cause acute inflammation of the pericardium. The diagnosis of nonspecific, benign pericarditis, recurrent in type, is in my opinion more consistent with the symptoms described in the case report. Acute benign pericarditis is a serofibrinous inflammatory process of the pericardium which may be recurrent and is chiefly noted in young people. Its cause is unknown. It has many characteristics of a reaction of hypersensitivity. As observed in this patient during her previous hospital admission and as reported in the literature,[14] cortisone sometimes induces dramatic improvement in acute benign pericarditis. Smith and coworkers[15] would probably think that the previous splenectomy in our patient favored the occurrence of the pericarditis. In their series of 11 children with thalassemia major upon whom a splenectomy had been performed, 5 developed acute benign pericarditis weeks or years after the operation. I have no personal experience on this question, but others[16] would debate the point that splenectomy in children may favor the occurrence of infections in general.

In conclusion, I think that the diagnoses of the patient should be those of *thalassemia major, transfusional hemochromatosis, and acute recurrent benign pericarditis.*

DR. G. F. VAWTER. Hyperuricemia may occur in adults with thalassemia, and symptoms suggestive of gout may occur. This is another type of injury, presumably chemical, and in cases of thalassemia, pericarditis, joint episodes, and hyperuricemia has been described, but the relationship of all these factors was not clarified.[17]

DR. M. BALDINI. This is also a possibility. From my experience, however, I do not think that hyperuricemia is of such a degree to create serious problems in childhood thalassemia.

DR. VAWTER. Did the x-ray show a pericardial effusion, Dr. Neuhauser?

DR. E. B. D. NEUHAUSER. There are several chest films. Recently, the cardiac silhouette was certainly tremendously but variably increased in size (Fig. 1). One fluoroscopic examination showed absence of cardiac pulsations. There are transient periods when congestion of the lungs and fluids in the costophrenic angles could be demonstrated. Between times the cardiac shadow never recedes to normal. At no time could we detect hemosiderosis of the lungs. It takes a considerable amount of iron deposit before we can recognize it.

DR. ANNA HAUCK. There is little to add to Dr. Baldini's fine discussion. Although this child had T-wave abnormalities on EKG, she never showed some of the more characteristic electrocardiographic signs of acute pericarditis. That is, the S-T segments were never markedly elevated.

DR. KEVY. Why do you think her pain followed transfusions on occasion?

DR. HAUCK. We have no good explanation but wondered if this might not some-

Fig. 1. Chest x-ray during an exacerbation of the pericarditis.

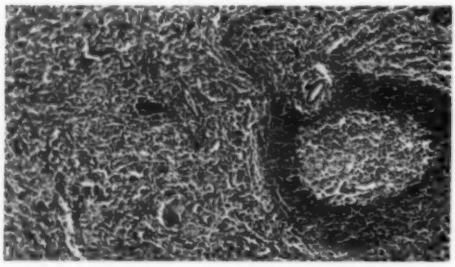

Fig. 2. Section of spleen showing the character of the follicles and the sinuses outlined by pigment-containing cells. (Toluidine blue and eosin, ×180; reduced ½.)

how be related to change in blood volume.

Dr. Vawter. The bone marrow of this patient, obtained 5 years ago, is hypercellular, with a high proportion of nucleated erythroid elements and very primitive cell types as well as considerable hemosiderosis. The spleen which was removed 4 years ago was 11 times the normal weight, very firm, and the thickened fibrous capsule was covered by fibrous adhesions. There is increase in trabecular tissue, but the principal increase in the firmness of the spleen appears to result from the hyperplasia of the reticulum of the red pulp. The sinuses of the red pulp are all lined by pigment-containing macrophages (much of this is iron pigment). As a result, the outlines of the sinusoidal channels are thrown into great relief (Fig. 2). In this case the splenic follicles are anything but decreased in number or in size; as may occur in thalassemia. Here they are quite large and active, with rims of immature cells forming so-called "inside-out follicles," which have been associated with patients having symptoms of hypersplenism. There are conspicuous islands of plasma cells. In addition, there are hematopoietic cells, including both myeloid and erythroid, and even some megakaryocytic forms. All of these findings are quite characteristic of treated Cooley's anemia and indicate considerable storage of iron in support of Dr. Baldini's diagnosis of hemosiderosis or transfusional hemochromatosis. In this particular spleen there is none of the peculiar nonpigmentary storage type of phenomenon which may be present in the spleen of patients with thalassemia.

Dr. Samuel R. Schuster. At operation the pericardium was obviously edematous and thickened (4 to 5 mm. in thickness). There was no striking amount of pericardial fluid present. There were some fibrinous adhesions from the pericardium and epicardium, and these gave way very easily. The pericardium stripped from the epicardium with ease and there was no advanced degree of fibrosis present nor was there marked evidence of constriction of the heart by involved pericardium. Therefore no decortication was necessary nor was exteriorized drainage considered likely to be of benefit.

Dr. Vawter. Material cultured at operation for ordinary bacteria or fungi and for tubercle bacilli showed no growth. Studies of the stool for presence of identifiable virus have been negative. In microscopic study of the pericardial biopsy, only about one-half of the thickest section of pleuropericardium represents the original structure. The pleura is lined by metaplastic serosal cells which contain pigment staining for iron (Fig. 3). Very little iron was demonstrable elsewhere.

As Dr. Baldini has reconstructed clinically, the thickening of the pericardium appears to be the result of serial episodes of involve-

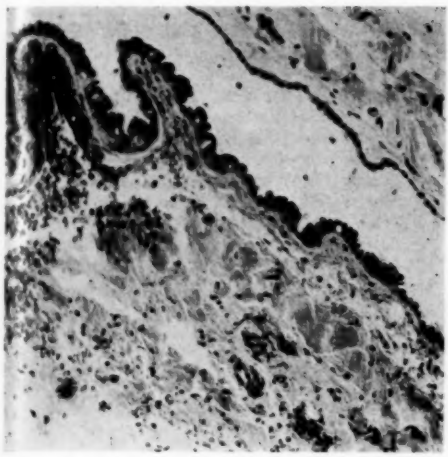

Fig. 3. Pleural surface of pleuropericardial biopsy. The serosa is metaplastic and some cells (left upper) contain granular cytoplasmic inclusions which stain for iron. (Toluidine blue and eosin, ×160; reduced approximately ¼.)

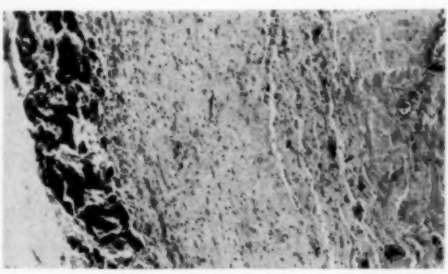

Fig. 4. Nearly full thickness of pericardial pleural biopsy. The pre-existing membranes occupy the right one-third of the field; the rest is proliferated connective tissues. The dark staining material at far left is fibrin. (Toluidine blue and eosin, ×140; reduced ½.)

ment (Fig. 4). The oldest and deepest consists of dense collagenous tissue and a few small blood vessels. Then comes an intermediate zone where the tissue is less dense and apparently younger, and, finally, surmounting this, a more recent and very active process characterized by the outpouring of fibrin. Noteworthy is the relative lack of any inflammatory cell infiltrate; only scattered lymphoid or plasma cells are found. If one bears in mind that the patient has had cortisone, he cannot completely exclude an infectious origin for the process, but it is difficult to explain the recurring nature of the lesion on this basis. The histologic features also are compatible with those of a chemical pericarditis or, more likely, as Dr. Baldini has suggested, a lesion of the nature of a process of hypersensitivity.

In summary, the clinical course and pathologic findings are compatible with *thalassemia major, hemosiderosis* (possibly a hemochromatosis-like picture), and recurrent *benign acute pericarditis* in a patient upon whom a splenectomy has been performed.

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COMMENTS ON CURRENT LITERATURE

Henoch-Schönlein syndrome—anaphylactoid purpura

THE HENOCH-SCHÖNLEIN syndrome is now regarded as a hypersensitivity phenomenon or as a type of allergic response similar except in degree of severity to that associated with such conditions as erythema nodosum and periarteritis nodosa. The characteristic visceral manifestations with purpura were first described by Henoch[1] in 1874, and the joint symptoms, arthralgia with purpura, somewhat earlier by Schönlein[2] in 1837. These manifestations appear to be part of a basic disease process involving capillary fragility without thrombocytopenia. The term syndrome has been preferred in describing this symptom complex because the illness represents a polymorphic systemic disease.[3] The condition can become manifest after the ingestion of certain foods or following upper respiratory infections, especially those associated with the presence of hemolytic streptococcus. Osler[4] called attention to the similarity between this disease in mild form and erythema multiforme and its similarity in severe form to serum sickness.

While the true incidence is unknown, the disease is not rare and appears to have been on the increase in recent years.[5] Males are affected about twice as often as females. Although the age of onset is rarely less than 1 year, cases in infants under 12 months of age have been recorded; the youngest authenticated case is probably that described by Philpott[6] in 1952 in a child of 8 months. The average age of onset falls between the ages of 3 and 7 years. Until recently little information as to basic pathogenesis has been available. A study of skin biopsies has suggested that the primary reaction involves an acute inflammatory exudate containing polymorphonuclear cells and round cells which surrounds the small blood vessels of the corium. Eosinophils may be present, and as a rule the number of erythrocytes observed varies with the severity of the purpura. The capillaries are involved characteristically, but pathologic changes in precapillary arterioles and a necrotizing arteriolitis with fibrin thrombi have been described. Lesions resembling those of this disease were induced experimentally[7] in animals by the injection of antibodies which had been produced against the endothelial cells lining their arteries.

The type of response seen in this anaphylactoid purpura has not been considered familial, although in many instances a family history of allergy has been obtained. In general, reports of more than 1 case in a family are not common; however, a few instances of the disease in siblings have been described. In a recent issue of the *British Medical Journal,* Towner[8] records the histories of 2 siblings, aged 5 years and 14 months. The second child is younger than the usual patient showing this syndrome. The author considers both these cases typical of the Henoch-Schönlein syndrome. In the 5-year-old girl, symptoms appeared soon after a second immunization against diph-

theria and pertussis. Prominent among the symptoms in this child were lower abdominal pain, intermittent pain in the calves of both legs, and pain in metacarpophalangeal joints. On admission to the hospital she was flushed and febrile; numerous petechial hemorrhages were observed on the hard and on the soft palate. Lymph nodes were palpable on both sides of the neck and in the axillae and groins. Vomitus and stool specimens contained some fresh blood. Some degree of hematuria was noted. In the second child, a boy 14 months of age, symptoms followed an episode of upper respiratory disease, complicated by an ear infection. At the time of hospital admission this child had marked purpura; hematuria had been present and fresh blood was seen in the stool for 3 days. On admission there was a left orbital hematoma, and an ecchymosis on the right upper eyelid. Edema of both hands and feet was present, and both knee joints were swollen. From a perforation of the left ear drum there was a purulent otorrhea. In both these children recovery was slow. The author is inclined to believe that "two different factors provoked the same hypersensitivity reaction—that is, the Henoch-Schönlein syndrome" and that "the type of hypersensitivity reaction, rather than the nature of its provocation," appeared to be "the common familial factor in these two cases."[8]

The occurrence of renal symptoms in anaphylactoid purpura and the possibility of renal sequelae are well recognized. According to published reports about 50 per cent of the children with this disease have proteinuria and hematuria of varying degrees at some stage. In the past, most of the histologic studies have been made on autopsy material from patients with severe symptoms who died in renal failure. A recent report of considerable interest concerns a study of the kidney lesions in biopsy specimens taken relatively early in the course of the disease. This study by Bergstrand, Bergstrand, and Bucht[9] has been reported recently. Following the suggestion of Derham and Rogerson[10] that the initial renal involvement in the Henoch-Schönlein syndrome may be "renal bleeding" rather than a true nephritis, the Scandinavian investigators felt that a study of early lesions by biopsy would give a more accurate impression of the disease process in the kidney, a better understanding of the nature of the disorder, as well as some information as to individual prognosis.

The 6 patients (2 boys and 4 girls) included in this detailed study correlating clinical manifestations with histologic study of the kidney were 7 to 15 years of age. All had anaphylactoid purpura and signs of renal involvement when the examination was made, and all were in relatively early stages of the disease. The method of renal biopsy was essentially the same as that employed for adults, described in 1954 by Kark and Muerhcke.[11] Adaptation of the method for use in children and certain technical details have been discussed previously by Bergstrand and Bucht.[12] Renal function was measured by endogenous creatinine clearance tests and by ordinary water-load and concentration tests. In some instances inulin and para-aminohippuric acid clearances were determined also. In all cases platelet counts, bleeding time, and coagulation time were carried out routinely, and all the results were considered well within normal limits. All of these patients had shown proteinuria, and 5 of the 6 had experienced relatively marked hematuria. None of them had shown clinical signs of renal insufficiency. In 4 of the patients with long-standing hematuria glomerular lesions were observed. These lesions were almost identical in the 4 patients with only minor degrees of difference noted among them. "In none of the biopsy specimens examined were erythrocytes observed in the glomerular capsules or in the tubular lumina. Nor could any bleeding be demonstrated in the interstitial tissue."[9] The authors feel that these observations do not sustain the opinion that the hematuria in anaphylactoid purpura represents only "a renal bleeding." No alterations were seen in the arterioles of the kidney. The authors are inclined to regard

the changes observed in the kidney as remnants of an inflammatory process, a glomerulonephritis. While in some instances the glomeruli showed changes of the "hyalinized-crescent" type similar to those seen in subacute hemorrhagic glomerulonephritis, the glomeruli involved in these cases of anaphylactoid purpura were few in number as compared with those seen in the typical case of acute hemorrhagic nephritis. The type of tubular change associated with the nephrotic syndrome was not encountered in these patients with anaphylactoid purpura. In 2 of the 4 patients a second renal biopsy was performed after an interval of about 2 years. No progressive histologic change was observed.

In an attempt to evaluate these observations the authors emphasize the preliminary nature of their studies: "At present it is only possible to state that in anaphylactoid purpura there may occur definite glomerular lesions, probably sequelae to a glomerulonephritis and associated with the clinical picture of persistent haematuria without signs of renal insufficiency."[9] While they look upon any renal involvement as potentially serious, they feel that "the prognosis of the kidney disorder associated with anaphylactoid purpura may not be unfavourable even in cases with persistent haematuria."[9] Further studies by these investigators are in progress.

RUSSELL J. BLATTNER, M.D.

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Books

Preventive Medicine in World War II, Vol. IV, Communicable Diseases.

Colonel John Boyd Coates, Jr., M.D., editor, Washington, D. C., 1958, Office of The Surgeon General, Department of The Army, 544 pages. Price $5.50.

The remarkable experience of our Armed Forces in the reduction of deaths from disease during World War II is presented in this authoritative volume published under the direction of the Office of the Surgeon General, Department of the Army. In all previous wars in which the United States was engaged with the sole exception of the experience of the American Expeditionary Forces during World War I, deaths from disease far outnumbered deaths from battle casualties. In World War II, the ratio of deaths from disease to deaths from battle casualties was 0.07 to 1.0!

Mortality and morbidity from diseases of the respiratory and gastrointestinal tract form the major part of the material presented in this, the fourth volume of a series concerned with preventive medicine in World War II. The 6 leading causes of death from disease in their respective order of frequency were tuberculosis, meningococcal meningitis, bacterial pneumonia, malaria, poliomyelitis, and infectious hepatitis.

The results of various control measures, including immunization, chemoprophylaxis, and sanitary measures are discussed in some detail. There are interesting historical notes; for example, Rommel's army in North Africa was better prepared to withstand Montgomery's troops than it was shigellosis.

The chapters on tuberculosis, diarrheal diseases, coccidioidomycosis, measles, meningococcal infections, and streptococcal diseases are especially interesting in relation to the epidemiologic data presented and discussed.

This text should be of real interest for those concerned with infectious diseases, sanitation, public health procedures, and the medical history of the greatest war our country has fought.

ROBERT H. HIGH, M.D.

Intussusception in Infants and Children.

Mark M. Ravitch, M.D., Springfield, Ill., 1959, Charles C Thomas, Publisher, 121 pages. Price $9.00.

This volume represents the first of a series of Pediatric Surgical Monographs to be edited by Mark M. Ravitch. The subject is covered completely in a clear and readable manner, and the diagrams and illustrations ably review the subject without the necessity of reference to the text. The author is well known for his interest and basic research in intussusception and especially for the development of a technique of reduction by hydrostatic pressure. He considers this method, "as much a surgical procedure as a reduction of a fracture by traction." The technique is meticulously described and beautifully illustrated as is the experimental work preceding its development, and the results of its use in other published series are recorded.

A historical review and analysis of current operative techniques are presented in a concise and lucid manner. Zachary's recommendation that if resection is necessary it should be a generous one so that the anastomosis is performed in undamaged bowel is especially pertinent. It is known that infants can survive and develop normally after resection of up to all but 26 cm. of their small intestine, exclusive of the duodenum, so that previous fears of nutritional difficulties, which may have led to inadequate resections, are unfounded.

Nineteen of the last 27 patients with intussusception in the author's series were operated upon and 3 were found to have a lead point (one was an inverted appendix). The incidence of Meckel's diverticulum, duplication of the intestine, polyps, cysts, or other lead points in the other 58 patients is not known. No instance of lymphosarcoma or other malignant tumors acting as a lead point of an intussusception is recorded by the author. Such lesions have been successfully resected by others and would have been missed if intussusception had been reduced by the barium enema technique.

The text includes detailed description and statistics of symptoms, signs, and other pertinent facts of intussusception. This reviewer would have made a subheading of the excellent paragraphs on preoperative treatment in order to emphasize them. In addition, mention might have been made of the fact that the initial rectal examination may not reveal blood because of a fecal bolus in the rectum which acts as a cork, and thus lull one into a false sense of security regarding the diagnosis. A more liberal and routine use of potassium chloride in pre- and postoperative fluid therapy than that described is practiced in many clinics.

Attempts to compare the results of therapy by hydrostatic pressure or immediate surgical attack are unrealistic. Patients who have irreducible intussusception and require operation are usually those whose lesion has been present for longer periods of time. Such patients naturally are sicker at the time therapy is undertaken and contribute heavily to morbidity and mortality statistics. Dr. Ravitch's opinion that reduction of barium enema with the use of his technique should be attempted in all cases of intussusception may be applicable in his well-organized institution. It still seems to this reviewer that if it is applied universally, unnecessary delays and unwise variations in the technique employed will endanger the lives of some children.

GEORGE P. PILLING, IV, M.D.

Infant Foods and Feeding Practice.

Herman F. Meyer, M.D., Springfield, Ill., 1960, Charles C Thomas, Publisher, 332 pages. Price $9.75.

In this book the author reflects on his more than 30 years experience in pediatric practice and presents a manual of infant feeding designed for those " . . . to whose lot falls the responsibility of directing the feeding of most well infants." This book is a sequel, not a reprinting nor a new edition, to a similar manual printed in 1952. Dr. Meyer reviews the fundamentals of infant nutrition, classifies infant foods now in general use, and discusses many concepts of infant feeding.

His chief contribution is to be found in chapters 5 and 6 where he has listed, with commentary, all of the milk mixtures for infants and carbohydrate additives and modifiers currently on the American market. In the remainder of this manual the author does not provide more genuine information on infant feeding than can be found in recent textbooks on pediatrics. The book does, however, include the author's conservative approach to infant feeding. The last chapter titled, "Clinical Trivia and Philosophic Observations in an Everyday Feeding Practice," expresses his disdain for various modern trends in infant care.

C. CHARLTON MABRY, M.D.

Correspondence

To the Editor:

Recently much has been written in the pediatric literature debating the necessity for the continued use of sterilizing measures in the preparation of formula. Obviously, the possibility of dispensing with sterile precautions was investigated because many modern mothers have complained about the bother of even the standard terminal method. For the past year and a half, I have used a modified terminal method which provides sterility and is simple and convenient.

Bottles and nipples are washed in the usual manner and rinsed thoroughly. The bottles are filled with the desired amount of water directly from the tap. The caps are put in place loosely and boiled 25 minutes, as in the standard method. Then they are removed and left at room temperature. Essentially, a sterile bottle of water has been made.

The precautions of either slow or rapid cooling to prevent scum formation is unnecessary, as is refrigeration, since there is nothing to spoil.

When a feeding is required, the mother merely takes the sterile bottle of water, adds either powder (which I prefer) or liquid, shakes it, and gives it to the baby. No heating is needed since it does not come out of the refrigerator. If a liquid formula is used, then the can must, of course, be kept in the cold once it has been opened. This may necessitate some warming.

The mother must be warned not to make up more than 6-ounce bottles of sterile water. If she puts in 8 ounces, there will be no room to add anything else. When an 8-ounce bottle is needed, several ounces of water can be boiled for 5 minutes. Meantime, the powder is added to the 6 ounces and then the boiled water to the 8-ounce mark.

The only precaution to be observed carefully is that if a bottle is not used within half an hour after adding the powder, then it must be discarded. If the baby, on the other hand, takes 1 ounce and decides to quit in 10 minutes and the mother is left with excess milk this can be refrigerated until the next feeding, since the ½-hour lag time for bacterial growth has not elapsed.

The advantages are numerous. Not only is it simple to make, but it does away with the need to go groping out to a refrigerator in the middle of the night, or going up and down stairs, or putting the bottles in an ice bucket in order to keep them nearby. Traveling and visits are easier. All that is needed are the bottles of water and the can of powder. I found the acceptance of mothers so good the girls were telling their friends about it.

BENJAMIN D. GORDON, M.D.
STRATFORD, CONNECTICUT

To the Editor:

I read with great interest the article by Gaisford in the February issue (J. PEDIAT. 56: 259, 1960). During the past 5 years I have had under my care 4 patients with essential pulmonary hemosiderosis and I should like to add the following points to its diagnosis and therapy. In my experience, when the child has severe anemia, a high reticulocyte count, widely distributed miliary lesions on the roentgenogram, a negative Mantoux reaction, characteristic recurrent attacks, and at times clubbing of the fingers, the diagnosis can usually be established by the demonstration of heart-failure cells. When the nature of the pulmonary lesion cannot be recognized with certainty and if the patient's life is in danger, pulmonary biopsy is indicated.

Unfortunately, by the time the diagnosis is made many patients have suffered irreversible damage to the lungs. For example, Soergel's case (Soergel, K. H.: Pediatrics 19: 1101, 1957) was admitted to the hospital on 15 occasions and was diagnosed only at the thirteenth one.

I think that essential pulmonary hemosiderosis is an immunoallergic disease (Steiner, B.: Essential Pulmonary Haemosiderosis as an Immuno-haematological Problem, Arch. Dis. Childhood 29: 391, 1954) and that splenectomy and treatment with prednisone is indicated in every case (Steiner, B.: The Value of Splenectomy in the Treatment of Essential Pulmonary Haemosiderosis, Acta Medica Acad. Sc. Hungar. 14: 211, 1959). The results obtained in 16 patients provide evidence that such therapy ensures a better chance of survival than does conservative management.

BELA STEINER, M.D.
POSTGRADUATE MEDICAL SCHOOL
BUDAPEST, HUNGARY

To the Editor:

Dr. Hubbard's article on page 554 of the April, 1960, issue of THE JOURNAL prompts my reporting experience in this office, since July, 1954, in the prevention of rheumatic fever and nephritis.

This is done by making throat cultures on all patients with upper respiratory infection and known streptococcal contacts. These cultures are planted 4 per plate and after 20 to 24 hours growth, we look for beta hemolysis, and then for gram-positive cocci in chains, in the beta hemolytic colonies. All patients with "strep" cultures are treated with Bicillin intramuscularly in amounts of 600,000 units if they weigh less than 60 pounds and with 1,200,000 units if they weigh more than 60 pounds. Erythromycin is usually used for patients sensitive to penicillin. In about 1,600 streptococcal infections (last count actually was 1,474 in April, 1959) since July, 1954, there have been no new cases of rheumatic fever or nephritis. I recognize that my follow-ups are informal, but I do consider them reasonably dependable, since this is a small community with a relatively fixed population, and cross reporting among physicians is common.

We offer this as a streptococcal screen only, and the charge made to the patient is $2.00 per culture. I have given lots of P.T.A. talks and made similar public appearances so that now many folks will drop in for cultures, even with the mildest upper respiratory infections, whether they feel they need an office call or not.

Of course one gets sick and tired of culturing throats and making phone calls, but our only new cases of nephritis or rehumatic fever in this 5-year period have been in uncultured and untreated patients or in patients who had symptoms so mild that they just did not come to our attention. In this period there actually have been 18 new cases of rheumatic fever in my office, and these had not been cultured or treated. If statistics of the past applied, I would expect to have seen 50 or 60 new rheumatic fever patients during that period also. This program has been more monotonous than difficult, and it seems to me that it has now demonstrated its value well enough that it would be worth encouraging other physicians to carry on a similar program.

SAM POBANZ, M.D.
ONTARIO, OREGON

To the Editor:

I have read with interest the first paper published in the section of Tropical Pediatrics in THE JOURNAL. The paper on hemorrhagic fever by Dr. Ethel Nelson (56: 101, 1960) is of great interest to Filipino physicians because, as far as we know, this form of hemorrhagic fever in children was first described in 1954 by Drs. Quintos and Lim of the University of the Philippines. In 1955 to 1956 the disease attained epidemic proportions, affecting Manila and the surrounding provinces only. In 1958 Drs. Quintos, Lim, and myself presented our findings before the First Regional Asian Congress of Pediatrics held in Singapore (Guerrero, R. M., De Leon, A., and Mendiola, F.: Observations on Philippine Hemorrhagic Fever, Philippine J. Pediat. 6: 4, 1957), giving our observations on this form of hemorrhagic fever, which we call Philippine hemorrhagic fever to distinguish it from the other forms described in the literature. A baffling aspect of hemorrhagic fever, besides the etiology which Hammon strongly suspects to be a form of dengue virus, was the sudden disappearance of the disease in the Philippines in 1957. Since then very few sporadic cases have been observed.

RENATO MARIA GUERRERO, M.D.
UNIVERSITY OF SANTO TOMAS,
FACULTY OF MEDICINE & SURGERY,
MANILA

News and notes

The Division of Cardiology, Department of Pediatrics, University of California at Los Angeles, announces a **training program in pediatric cardiology** with instruction in clinical and basic science for those interested in academic medicine or the practice of clinical cardiology.

The 2-year minimum program is designed to meet the qualifications of the specialty board in pediatric cardiology. Instruction in clinical cardiology will include patient care, electrocardiography, phonocardiography, vectorcardiography, cardiac catheterization, angiocardiography, dye dilution, pulmonary dynamics, and other useful techniques. Instruction in basic cardiology will include physiology, biophysics, biostatistics, biochemistry, nuclear physics, and medical writing as these relate to cardiology. Research will be required of each trainee.

Graduates of Class A medical schools who have completed pediatric training acceptable for certification by the American Board of Pediatrics are eligible. Stipends begin at $5,500 per year, with additional allowance for dependents. Interested applicants should write to Arthur J. Moss, M.D., Cardiology Training Program Director, Department of Pediatrics, University of California at Los Angeles School of Medicine, Los Angeles 24, Calif.

A memorial to Dr. A. Graeme Mitchell will be established at the University of Cincinnati. The first stage of a campaign to raise funds will be a lecture series at the University on topics of Dr. Mitchell's major interests, including his avocations of writing and art. A biographical sketch prepared by John F. Cronin, former Cincinnati newspaperman, will be given to each donor. Contributions may be made through the U. C. College of Medicine. Members of the committee were residents during Dr. Mitchell's tenure at Children's Hospital, Cincinnati.

Dr. Mitchell, who died in 1941, was Professor of Pediatrics at the University College of Medicine, medical director and chief of staff of Children's Hospital, director of the Children's Hospital Research Foundation, and director of pediatrics and contagious diseases at Cincinnati General Hospital. He was co-author with J. P. Crozer Griffith of the textbook *Diseases of Infants and Children*, now edited by Waldo E. Nelson as *Textbook of Pediatrics*.

The American Board of Pediatrics, Inc., certified the following diplomates at New Orleans, Louisiana, on March 25, 26, and 27, 1960:

Agricola, Frederick Theodore, Jr., 1011 Forrest Avenue, Gadsden, Alabama

Alexander, E. Russell, Communicable Disease Center, 50 Seventh Street, Northeast, Atlanta 5, Georgia

Aplin, Elizabeth Rowland, 3095 Halesworth Road, Columbus 21, Ohio

Batterson, Robert E., 3051 Northwest Boulevard, Columbus 21, Ohio

Brown, Claude H. B., 921 14th Northwest, Ardmore, Oklahoma

Burns, M. Dorothy, 37 Hardwick Avenue, Piedmont 11, California

Canby, John Price, 75th Station Hospital, APO 154, US Forces, New York, New York

Cherry, Arthur Charles, Jr., The Topeka Medical Center, Tenth and Fillmore, Topeka, Kansas

Christy, Raymond Arthur, Jr., Smith Glynn Callaway Clinic, 1211 South Glenstone, Springfield, Missouri

Colletti, Ben Matthew, 601 Ninth Avenue, Port Arthur, Texas

Conner, Oscar Weir, III, 906 North State Street, Jackson 1, Mississippi

Culpepper, Robert Campbell, 1312 Albert Street, Alexandria, Louisiana

Davis, David Winningham, 6213 10th Avenue, Kenosha, Wisconsin

Deshautreaux, Ernest Edward, 2202 26th Street, Kenner, Louisiana

Dodson, Albertus F., 115 North 1st Street, Brainerd, Minnesota

Dunagin, James L., 1532 Tulane Avenue, New Orleans, Louisiana

Eckert, Herbert L., USNH, Navy No. 3923, C/O FPO, San Francisco, California

Fruge, Bernard C., 1000 Nile Street, Eunice, Louisiana

Gamble, Charles Edward, 2524 Washington Avenue, Waco, Texas

Grogan, Fred Turley, Jr., Frank T. Tobey Memorial Children's Hospital, 860 Madison Avenue, Memphis 3, Tennessee

Grossman, Elmer R., 1936 Los Angeles Avenue, Berkeley 7, California

Hardey, C. Eugene, 600 West Park Row, Arlington, Texas

Hunt, Samuel L., 10023 Garland Road, Dallas 18, Texas

Hutchins, Vince L., 1880 Vallejo Street, #2, San Francisco 23, California

Jenkins, Madden Douglas, 5211 Rexton Lane, Dallas 14, Texas

Jockin, Hubert, Children's Hospital of D. C., 2125 13th Street, Northwest, Washington, D. C.

Johnson, James Trimble, P.O. Box 1332, Lumberton, North Carolina

Johnston, Carl Mason, 5010 Franklin Road, Boise, Idaho

Jones, James David, Box 3213, Duke Hospital, Durham, North Carolina

King, E. Henry, Sunland Training Center, Gainesville, Florida

Kittredge, George Shaw, 1212 South 11th Street, Tacoma 5, Washington

LaTourrette, Margaret W., 2076 Kearney Street, Denver 7, Colorado

Lehmann, Louis C., 602 Orleans Street, Natchez, Mississippi

Leovy, William A., 3019 Marquette, San Diego 6, California

Lester, Richard L., Jr., 719 Franklin Street, Huntsville, Alabama

Liddle, William Dyer, Jr., 2301 Fall Hill Avenue, Fredericksburg, Virginia

Lies, William, III, 509 West Main Street, Dothan, Alabama

Lynch, Dorothy R., 808 Joliet Street, West Chicago, Illinois

Lyon, Franklin L., 3250 Northwest Boulevard, Columbus 21, Ohio

McKell, Joseph Power, 601 DeLeon, Tampa 6, Florida

McLaughlin, Lloyd A., Jr., 501 North Jefferson Davis Parkway, New Orleans 19, Louisiana

Moore, Donald Barclay, 1557 Twenty-fourth Street, Boulder, Colorado

Morris, Clifton T., Jr., 3943 Louisiana Avenue Parkway, New Orleans, Louisiana

Oglesby, Allan Campbell, The Medical Group, 1133 Punchbowl Street, Honolulu 13, Hawaii

Ooghe, Arthur Tallant, 6885 Brockton Street, Riverside, California

Pabst, Paul James, 2311 Ardmore Lane, Manhattan Beach, California

Park, David Riggs, 3238 Reba Drive, Houston 19, Texas

Parke, James Clifton, Jr., 4 Rivercrest Drive, Portsmouth, Virginia

Peeler, Milton B., 719 Franklin Street, Huntsville, Alabama

Pepper, Carmen Isabel Posada, 3800 Octavia Street, New Orleans 25, Louisiana

Robinson, Nan Elizabeth, 601 East Spring Street, New Albany, Indiana

Royal, Arnold, 1714 11th Avenue, South, Birmingham 5, Alabama

Sessums, John Valton, Jr., Dakota Clinic, Fargo, North Dakota

Shoptaugh, A. Glenn, Jr., USAF Hospital, Sheppard Air Force Base, Texas

Skyer, Roslyn, 3518 North Flagler Drive, West Palm Beach, Florida

Spach, Madison Stockton, Duke Hospital, Durham, North Carolina

Stein, Michel David, 48 East Santa Clara, San Jose, California

Steinborn, Kurt E., Porterville State Hospital, Porterville, California

Sztramski, Geraldine Anne, 1777 Bellflower Boulevard, Long Beach 15, California

Thannisch, George Edward, 1121 Ellis Avenue, Lufkin, Texas

Thompson, Lee H., 650 East Green Tree Road, Milwaukee 17, Wisconsin

Torsney, Jerome M., 737 Broad Street, Clifton, New Jersey

Tracy, Frank W., 565 North Grant Street, Hinsdale, Illinois

Ulich, Konrad Heinrich, 17710 San Fernando Mission Boulevard, Granada Hills, California

Waiches (Baker), Helen M., 1106 Marygene, Columbia, Missouri

Walker, James William, 1645 Clemson Road, Jacksonville, Florida

Warner, Forrest Stanley, USAF Hospital, Clark Air Force Base, APO 74, San Francisco, California

Weinfurtner, William Howard, 6950 Brockton Avenue, Riverside, California

Weinstein, David B., 7452 B O'Reilly Street, El

Paso, Texas
Whitaker, Jo Anne, 5323 Harry Hines Boulevard, Dallas 19, Texas
Yount, Harold Alexander, 1500 South Olive Avenue, West Palm Beach, Florida
Yu, Julia Shih-fan, 1714 Washington Boulevard, Maywood, Illinois
Zion, Thomas E., Lackland USAF Hospital, Lackland Air Force Base, Texas
Zwirn, Benjamin H., 18 Montclair Avenue, Florissant, Missouri

SPECIAL FOREIGN CERTIFICATES:

Canosa Martinez, Cipriano, Spain
Shawky, Yehya Abdel-Karim, Egypt

The Journal of Pediatrics Educational Foundation announces the following Lectureships for 1960:

Domestic Lecturers and medical school departments of pediatrics where they will visit: Dr. Katherine Dodd, Yale University; Dr. Harry H. Gordon, University of Iowa; Dr. Charles A. Janeway, University of Manitoba; and Dr. Donald E. Pickering, University of Washington.

Domestic Lecturers participating in residency training programs are Dr. Alton Goldbloom at Springfield, Massachusetts, General Hospital, and Dr. Julius B. Richmond at Akron, Ohio, Children's Hospital.

As Foreign Lecturer, Dr. John Lind, Professor of Pediatrics of the University of Stockholm, will visit the pediatric departments of each of the following medical schools: University of Buffalo, Einstein in New York, University of Georgia, McGill University, and University of Vermont.

A new society, the **East Bay Pediatric Society**, was formed last November for pediatricians of Alameda and Contra Costa Counties, California. Officers elected were president, Edward F. Carlson, M.D., Oakland, and secretary, Marianne Schour, M.D., Oakland.

Effective July 1, 1960, the fees for first **examinations of the American Board of Pediatrics** will be $125. The fees for second and third oral examinations will be $75.

The oral examination session originally scheduled for Miami in December will be held in Washington, D. C., Dec. 1 to 4, 1960.

EDITOR'S COLUMN

Measles vaccine

SINCE the introduction of vaccination against smallpox, the elimination of epidemics of infectious disease by means of prophylactic inoculations has been a major objective of physicians. Phenomenal success has attended the efforts of microbiologists in the development of such measures as diphtheria and tetanus prophylaxis and of public health physicians in the dissemination of information and the implementation of such programs. As more and more viruses are isolated and their characteristics studied in the laboratory, virologists and immunologists are discussing the technical possibility of developing prophylactic measures against an increasing number of the infections that plague mankind. There are, however, giant steps between developing an antigen that produces antibodies in animals or even in human beings and the use of such an antigen as a vaccine for mass inoculation. Some of the criteria to be met are: (1) can such a vaccine induce lifelong or very prolonged immunity? (2) does the vaccine produce reactions which are discommoding if not dangerous? (3) how much does the population want such prophylactic measures, or, in other words, how obvious to an educated public is the need for such a step?

The idea of a prophylactic regimen against measles was presented over 40 years ago by Herrman in New York. This physician, over several years from 1914 to 1922, explored the transmission of measles to infants through the nasopharyngeal route by inoculating nasal mucus taken from patients during the preeruption stage. He found that infants under 5 months did not develop mild measles and were not immune to later exposure, but by the end of the fifth month of life 50 per cent of 165 infants developed a fever and scattered spots resembling measles. He followed 75 of these for 4 to 8 years and only 5 developed measles despite intimate exposure of 45 of them. Furthermore, 36 of such infants resisted infection when challenged with measle-containing mucus.[1]

Stokes and associates[2] inoculated 215 children with egg-grown virus and found that 74 per cent developed mild measles after inoculation. Maris and others[3] reported the incidence of measles in 46 children vaccinated with early egg-passage measles virus. Chance exposure of 22 of them up to 1 year after vaccination resulted in infection in only 32 per cent (7/22), while challenge with blood from active cases of measles resulted in only 46 per cent infection (11/24). However, in later reports Maris and colleagues[4] found that the incidence of measles in 497 children vaccinated with later-passage egg virus was 69 per cent following at least 1 major exposure, as compared with 88 per cent among 50 unvaccinated control children, indicating that vaccination produced only a slight degree of protection. Only one of the group vaccinated with early

pasage virus was followed continuously. She escaped measles from several exposures during childhood only to contract the disease in early adulthood.

In the paper by Dolgin and colleagues,[5] published elsewhere in this number, several points in favor of an immunizing procedure against measles are raised. Among these are (1) the ill effects of measles encephalitis and (2) the effects of measles on the fetus. Their experience with attenuated virus given subcutaneously was encouraging in that even with a very small dose of egg-grown vaccine antibodies were produced in 3 children. However, 8 of 10 children inoculated with this low passage egg-grown virus, regardless of dose, developed reactions resembling mild measles, a similar experience to that of Stokes and others. It is more encouraging to note that the chick embryo tissue culture vaccine produced antibodies without evidence of an infection. Required, of course, is the establishment of some correlation between antibodies present 3 to 4 weeks after vaccination and a permanent immunity, an answer which only time can provide. It would be unfortunate to postpone measles to adulthood when the effect on the fetus would also have to be reckoned with. The authors rightly raise the possibility that a mild measles reaction to vaccination might in itself induce an encephalitis. Until such a possibility is ruled out, it would appear unjustifiable to introduce a prophylactic procedure, which might in itself lead to encephalitis, in order to protect the 1 in approximately 2,000 patients with measles who dies or is disabled from encephalitis. Such disability as fever and a rash and the remote risk of encephalitis might be tolerable, as are the risks that accompany smallpox vaccination, if measles were a serious cause of infantile mortality as it still is in such places as West Africa.[6]

Naturally every effort should be made to explore the possibilities of producing a measles vaccine for use in areas of serious hazard. Before it could achieve wide acceptance in this country, however, it would at least have to satisfy physicians and the public at large that it could induce a lifelong immunity, not just a temporary postponement of an attack of measles from childhood to adulthood, and that reactions of the magnitude encountered to date were not a necessary accompaniment to the production of permanent immunity.

T. F. MC NAIR SCOTT, M.D.

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The right word in search of a doctor

IT HAD to be Mark Twain who wrote, "The difference between the right word and the almost right word is the difference between lightning and the lightning bug." One has but to attend almost any conference of physicians to realize how adept many of them are at by-passing or misusing the right word. I am not considering the "Good Old Doc" who informed me, "He ain't got no pneumonie, I don't think." Only a linguistic miracle could save him.

I am thinking of some, although by no means all, of those whose learning entitles them to teach the young in our medical schools, and who are rightfully leaders of our top-flight medical conventions. A goodly number, of course, carry the perfectionism essential to good medicine into the realm of self-expression. All honor to them!

But it must be admitted that we have here an all-too-noticeable trend. It may even be unavoidable. It has been said by several observers that our fund of knowledge doubles every 10 years. Of medical science it might now be correct to say that it triples with each decade. Keeping up with this happy if oppressive burgeoning of medical investigation is essential to the proper care of our patients. It is also essential to our students who must pass the many examinations designed to disclose what they do and do not know. Small wonder that Kultur, and with it self-expression, does well to have survived as well as it has. Its place is necessarily secondary. But even in our "best" medical circles, how often it falls flat on its face! Now and again I hear a colleague ask the rhetorical question, "Do I make myself clear?" To shout, "No!" might at the same time be both indicated and out of order.

Let this piece be regarded as a sequel to that medicoliterary gem by my friend the late Dr. Jean V. Cooke.[1] In it he paid his respects to a selected list of words commonly *mispronounced* in otherwise erudite medical circles. My purpose is to set before any who might be interested certain additional, currently *misused* words and expressions, plus a few choice violations of orthoëpy.

It is all very well for a poet like Robert Browning to write of "fancies that broke through language and escaped." Even he agreed that some of his own fancies could be understood only by himself and God. But it is positively dangerous for those who contribute to, or teach, or practice medical or other science to (a) indulge in fancies or (b) to let their scientific facts break through language and escape in such remarks as the former "happens seldom"; the latter "happens all the time."

First, consider the more outrageous conflicts between singular and plural:* "The accumulated data suggests . . . " (from the March, 1960, issue of one of our pediatric journals). The plurality of "data" escaped both author and editor.

A Health Commissioner writes, "Last year 543 persons died in ___ City of an accident," meaning many accidents, not just one holocaust. Thus he did violence to his own statistics.

From the Department of Pediatrics, Washington University School of Medicine, and the Homer G. Phillips Hospital, St. Louis, Mo.

*The day after submitting this article (April 10, 1960) I read Dr. Harry Goldblatt's excellent letter to that spirit akin to ours, Dr. Joseph Garland (New England J. Med. 262: 633, 1960) in which he pays his respects to certain "singular plurals." Obviously, he is himself more than one "Goldblatt phenomenon," and is highly qualified as an apostle (evangelist) of the Right Word. I can only hope he will write "stet" to my screed.

Or (another pediatric journal), "The cause of these conditions are not apparent." No comment. "A foci of infection." "A diagnostic criteria." "A polypi." This last was used consistently by a former teacher of mine. How singular can plurals be?

Rather more beguiling are certain *spoken* plurals which do lip disservice to the classics: Yes, the plural of "basis" is "bases," pronounced "basees"; the plural of "diagnosis" is "diagnoses," pronounced "diagnosees." But hearken now to four innocent words whose plurals are so often stretched to virusees, abscessees, processees, and fetusees. Such violators are obviously linguistic *Jackassees.*

Now for a few of the more revolting redundancies: "Pericardial friction rub": this is by way of becoming universally accepted. Does friction need a rub added to it, or a rub friction?

"Cut section": O pathologists! A section of anything, even of a pie, is inevitably cut.

"Reduplication": think it over as you say it. Didn't you mean duplication? A reduplicated second heart sound would be positively staccato!

Only in the past decade has the use, or abuse, of "too" for "very" become rampant upon the printed page or the lecture platform. "Penicillin is not too reliable in the treatment of that infection." Just when does a remedy become *too* reliable?

"She's not doing too well today." Unless you've taken a dislike to her, she could hardly do *too* well, could she?

Finally, a few random linguistic sins which so easily beset us medicos: Consider, I pray you, the doctor who says, "He hasn't got a temperachoor, I don't think." Yes, he meant to say, "I don't think he has a fever." But how much better if he'd said it!

"Dilatation." Surely, dilation would stretch any orifice just as widely! Let the word go the way of "preventative" and "therapeutical." We don't use the verb "to dilatate," do we?

*"DIS*charge." This pronunciation when the word is used as a verb ("He was DIScharged from the hospital") is completely unacceptable. As a noun (a purulent DIScharge, for example) it is given second pronunciation, disCHARGE being preferred.

I hope you have winced properly, perhaps privately, on hearing "premachoor, immachoor, adventissue, terriomyacin, streptomyacin."

I trust that the foregoing does not lay me open to the base and baseless charge of purism. I am fully aware that in certain instances, the dictionary (for our purposes the Merriam-Webster unabridged, plus the medical dictionaries) has yielded to usage and changed "preferred pronunciations" from, say, "pahliomyelitis" to "poliomyelitis," and even "glaDIOlus" to "glaDIOHlus." Even I have yielded to usage in accepting the etymologically "mixed" word "pediatrician" instead of the better "pediatrist." For, lo, the latter has become stilted, even to the point of conspicuousness! This is indeed less important than good usage, or what Dean Briggs loved to call "Clean English."

Yes, of course, when we are medically or surgically sick, we should prefer to be in the care of the doctor who knows most about etiology, diagnosis, and therapy, however lacking he may be in syntax and orthoëpy. But surely it is not amiss to plead for graduates in medicine who, like George Eliot's version of Stradivarius, have "an eye that winces at false work and loves the true," who will not be found careless in use of language, any more than in use of stethoscope, head mirror, or electrocardiogram.

PARK J. WHITE, M.D.
5879 CABANNE AVENUE
ST. LOUIS 12, MO.

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